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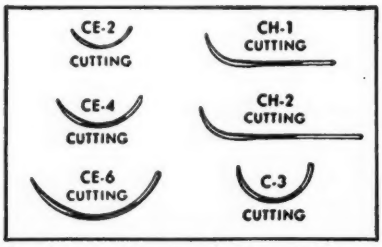

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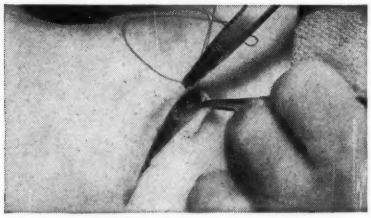

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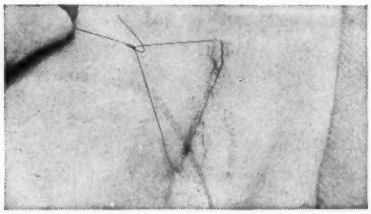

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 99 AUGUST, 1954 NUMBER 2

ACUTE ARTERIAL INJURIES

WILLIAM G. WHITAKER, JR., M.D., F.A.C.S., WALTER FAUST DURDEN, M.D., and IRA A. FERGUSON, M.D., F.A.C.S., Atlanta, Georgia

INJURIES to major arteries are not frequently encountered in the peacetime practice of surgery. Only during modern warfare with its appalling number of casualties can adequate data be collected on the management of these cases. Much of the information gained during World Wars I and II concerns itself with the immediate results of sudden interruption of major arteries. The monumental studies of DeBakey and Simeone and Rose, Hess, and Welch are important in their statistical analyses of acute vascular injuries of World War II. These studies attest the disastrous consequences that often follow occlusion of major arteries of an extremity.

Toward the end of the present fighting in Korea, favorable reports appeared on direct repair of injured arteries with restoration of their continuity. Previously, ligation had been the treatment of choice in that restorative surgery had not been satisfactorily adapted to war wounds and to front line military situations. Jahnke and Seeley have shown that reparative surgery may be, and should be carried out in forward installations. They repaired 34 consecutive major arteries without regard for time lag if the extremity appeared viable. Only 3 of these patients subsequently required amputation. This represents an amputation rate of 8.8 per cent as opposed to a rate of 53 per cent for a World War II series, reported by DeBakey and Simeone, in which the injured arteries were ligated.

Inasmuch as the majority of civilian surgeons are occasionally faced with an acute arterial injury, it is the purpose of this paper to discuss certain principles in the diagnosis and management.

Of primary concern are the *critical* or major arteries of the extremities, the axillary and brachial in the upper, the iliacs, femoral, and popliteal in the lower. These vessels are so categorized in that their sudden interruption is attended by gangrene in an appreciable number of instances. Obviously, under ideal circumstances, in certain specific cases, any of these arteries may be ligated without immediate untoward results. Unfortunately, at the time of decision as whether to ligate or repair the injured artery, the situation is not often ideal, nor does one have assurances that deliberate interruption may not prove disastrous. Rose, Hess, and Welch found the incidence of gangrene following ligation of major arteries in war wounds as follows: axillary 40 per cent, brachial 31 per cent, popliteal 77 per cent, and femoral 82 per cent. The incidences of gangrene recorded by DeBakey and Simeone were: axillary 43 per cent, brachial above the profunda 55.7 per cent, brachial below the profunda 25.8 per cent, common iliac 58.8 per cent, external iliac 46.7 per cent, common femoral 81.1 per cent, superficial femoral 54.8 per cent, and popliteal 72.5 per cent. These figures are significant in that they represent

From the Whitehead Department of Surgery, Emory University School of Medicine, and the Grady Memorial Hospital, Atlanta, Georgia.

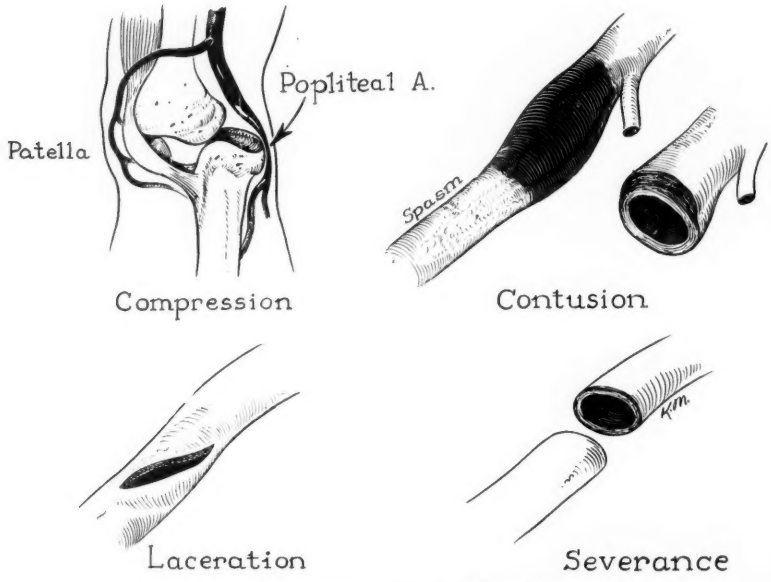


Fig. 1. The common types of arterial injuries.

the immediate loss of some part of the limb. It is known that a sizable number of those injured, while escaping immediate amputation, have degrees of arterial insufficiency varying from intermittent claudication to ischemic fibrosis and contractures. It is forcefully apparent that arterial continuity should be restored whenever possible in order that both the immediate and the long term results of treatment may be satisfactory.

An artery may be damaged by contusion, compression, laceration, or complete severance (Fig. 1). Compression is noted in the presence of dislocations and fractures, perhaps most frequently about the knee and elbow. In such instances, the vessel may be stretched over bone elements involved in a dislocation and is attended by vasospasm of variable intensity. Contusion of an artery may simulate complete transection to the extent that the exact character of the injury is appreciated only when the vessel is visualized at operation. Vasospasm is often segmental and intense when there is intimal damage with intraluminal clots, or when there is extravasation of blood within the vessel wall. Vasospasm in these cases is often independent of sympathetic nervous system stimuli and is due to contraction of the intrinsic muscles of the vessel. This is borne out by persistence of vasospasm following denervation, either by paravertebral block or high spinal anesthesia.

Laceration or partial severance of an artery is usually associated with large, tense hematomas in closed spaces or exsanguination in the wound with free outside communication. Partial division of an artery prohibits retraction of the ends into the adjacent soft tissues where bleeding could be arrested. Complete division of an artery may allow the vessel to retract into muscle masses where clotting often occurs earlier. In such cases, the hematoma will be smaller than those resulting from incomplete division.

Early correct diagnosis of arterial injuries rests primarily on a high index of suspicion on the part of the examining surgeon. Oftentimes, the patient is first seen in shock, hence, it is difficult to discern differences in the feeble to absent pulsations of cold, moist extremities. A regular blood pressure cuff, or better an oscillometer, may be an aid in recognizing di-

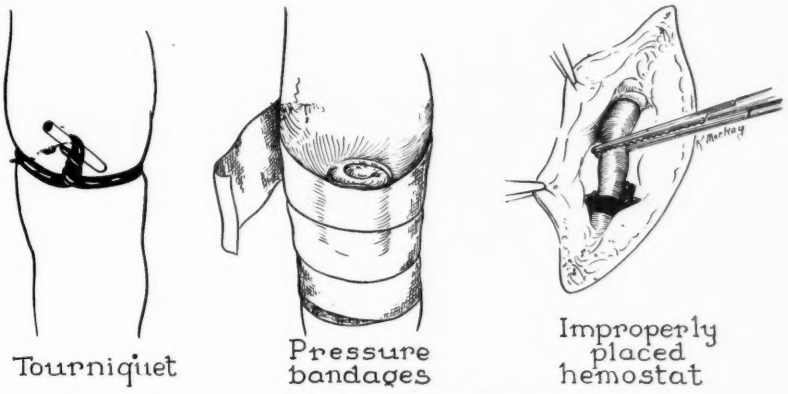


Fig. 2. Methods of controlling hemorrhage.

m ished pulsations in an injured extremity. T e site of the injury, the presence of fracture, or neurologic injury in the neighborhood of a m jor vessel is important. As the patient imp ves under supportive therapy, differences in the two extremities are more fully appreci ted. It should be borne in mind that peripheral pulsations may be present for an indefinite period of time following incomplete lacerations. Hematomas in the axilla, groin, thigh, or popliteal space usually denote arterial damage. Finally, subjective findings such as tingling, numbness, or hyperesthesia may be present. Intense pain in an injured extremity may be the result of ischemia and thus call attention to unsuspected vascular damage.

In a considerable number of arterial injuries, hemorrhage constitutes the immediate hazard. In certain instances, all efforts are directed toward saving life, the limb being of secondary importance at the time. Immediate arrest of bleeding is mandatory but some thought should be given preservation of the remaining collateral vessels (Fig. 2). The tourniquet is unexcelled in its ability to control bleeding, but is equally as vicious in occluding and damaging collateral pathways. A local pressure dressing utilizing gauze sponges and some type of wrap around bandage is superior in that some collaterals may be spared to nourish an already ischemic extremity. On occasion, hemostatic clamps may be used when the site of bleeding is plainly visible. Great care should be taken in applying the clamp lest the artery be further damaged by crushing it at some distance from the site of actual injury. Such instances may necessitate arterial resection and anastomosis where simple suture of the original laceration may have sufficed.

Shock from hemorrhage should be treated early with adequate blood replacement. Plasma, dextran, or dextrose solutions should be used to maintain blood volume until whole blood is available. Restoration of circulating blood volume is of great importance in maintaining collateral pathways and relieving some elements of vasospasm in the injured limb. Obviously, antibiotics and protection against gas gangrene and tetanus should be included in the early measures of resuscitation. The use of peripheral vasoconstrictors in an effort to raise and maintain normal blood pressure is contraindicated. Constriction of the minute collateral vessels may further jeopardize the extremity.

Surgical intervention should be undertaken as soon as the patient is thought capable of withstanding the procedure. It is not essential that the patient be brought to a state of normotension before definitive measures are taken. The time lag between injury and repair has unequivocal influence on the final results of treatment. This fact has been demonstrated repeatedly by many investigators. If

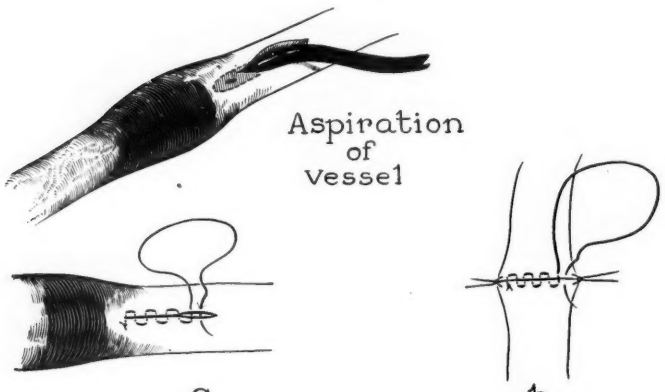


Fig. 3. Management of arterial contusions. a, Arteriotomy for exploration for clots. b, End-to-end anastomosis following resection of contused area if thrombosis had occurred prior to surgery.

an extremity appears to be viable, reparative surgery should be considered regardless of the time interval. Adequate surgical exposure is essential in the management of vascular injuries. Extensile exposures advocated by Henry are excellent and are applicable in nearly all cases. The artery is exposed, isolated, and controlled, both proximally and distally, by the application of small rubber shod bulldog clamps or twisted umbilical tape. Special arterial instruments are excellent if available but are by no means necessary. Examination of the arterial wound will now determine the type of restoration needed. Débridement of the surrounding soft tissues should be accomplished at this point in order to prevent excessive manipulation after the artery has been repaired or a graft inserted.

Displacement of bone fragments, or tight hematomas in closed fascial spaces may occlude an artery by compression. Correction of the etiologic factors with exploration of the vessel is nearly always necessary. Early operative intervention may be expected to produce good results in most cases.

Contusion of an artery may be accompanied by thrombosis at the time of surgery. Often the injury is confined to the intima and the media with the adventitia appearing normal, or at most, demonstrating mild to moderate extravasation. Smith has demonstrated that decreased blood flow in the presence of only slight intimal damage may produce thrombosis. If the artery is not found to be pulsating distal to the contused segment, it should be incised longitudinally in a search for clots (Fig. 3). If thrombosis is found, the area should be resected and treated as a complete severance with loss of arterial substance.

Partial severance or laceration should be débrided and repaired as such. The laceration may be tangential, transverse, or longitudinal. The severed edges should be approximated with everting mattress sutures along the direction of the laceration (Fig. 4). These sutures, fine silk on curved, atraumatic needles, should include all layers of the vessel and may be oiled to prevent tearing of the vessel wall. A saline soaked sponge is placed about the repair and the bulldog clamps are released. If leakage occurs after the sponge has been held in place for 5 minutes, another suture or two will often suffice in arresting this bleeding.

Complete division of an artery is treated by end-to-end anastomosis (Fig. 5) if there is little loss of vessel wall, or by vein graft if loss of tissue precludes apposition of the débrided ends without tension. It may be necessary to mobilize the artery 10 to 15 centimeters in either direction in order to accomplish anastomosis. Such mobilization at times will of necessity sacrifice certain collateral vessels.

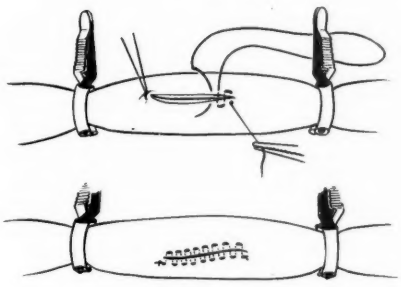


Fig. 4.

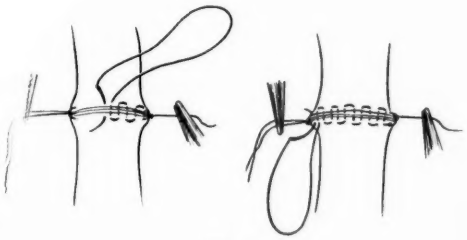
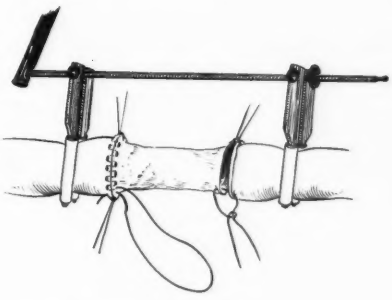


Fig. 5.



Vein Graft

Fig. 6.

Fig. 4. Repair of laceration.
Fig. 5. Repair of severance by end-to-end anastomosis.
Fig. 6. The lower figure demonstrates balloon effect noted when blood flows through the graft.

Transections due to gunshot wounds require more extensive vessel débridement. It has been shown that disruption of the architecture of the vessel wall may extend 1 to 2 centimeters from the actual site of wounding. Thorough mobilization is mandatory if end-to-end suture is to be accomplished in these cases. The rubber shod clamps are temporarily released just prior to repair in order to determine the presence or absence of thrombus formation. Gentle suction with a rubber catheter will usually restore patency of the vessels if local thrombosis has occurred. The ends are irrigated with saline-heparin solution and the anastomosis begun with 2 bisecting stitches which are joined with a continuous everting mattress suture. Again, gentle pressure with a moist gauze sponge will stop most leaks at the site of repair. If excessive arterial loss is present, a vein graft may be used (Fig. 6). The vein may be the concomitant vessel, the cephalic or the saphenous. The graft should be reversed to prevent obstruction of blood flow by its valves. It is sutured in place in the exact manner of anastomosis as described previously. It is absolutely necessary that the sites of repair, and particularly the site of a vein graft, be covered with adjacent tissues and the vessel not be allowed to bridge an open space. It may then be necessary to transplant, or to sacrifice, a muscle belly in order to cover the injured vessel. If flexion of parts of an extremity is necessary in order to allow repair to be made without tension, this position must be maintained by the immediate application of a plaster shell or similar device. The patient is placed on a flat bed with the extremity in a horizontal position at room temperature. Local heat should be avoided. Elevation should be used only if considerable edema is present, and then should be on a temporary and intermittent basis.

The use of sympathetic blocks or sympathectomy following the arterial injury remains an unsettled question. It has been our policy to use paravertebral procaine blocks almost routinely, and to repeat them at regular intervals, depending on the response and the particular need of the individual patient. Lumbar sympathectomy has been done in several instances immediately following arterial repair. This procedure should not be accepted

as routine in that some of these patients are not good risks for further surgery at the time of the acute vascular injury.

In a similar manner, anticoagulants, particularly heparin, have been used in a considerable number of cases following arterial repair. Further investigation will be required to confirm the advantages of anticoagulants; our patients have not appeared to be greatly benefited by their use.

SUMMARY

General principles in the diagnosis and management of acute arterial injuries of the extremities are discussed. Pertinent data concerning wounds of arteries occurring in World War II and the Korean Conflict are presented, emphasizing the promising end results of those patients receiving reparative surgery near the front lines.

The techniques of operative repair of damaged arteries are described.

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THE GENESIS OF GASTRIC AND CERTAIN INTESTINAL DIVERTICULA AND ENTEROGENOUS CYSTS

N. G. B. McLETCHIE, Ch.B., M.D., J. K. PURVES, M.D., and
R. L. DEC. H. SAUNDERS, Ch.B., M.D., F.R.S.E., Halifax, Nova Scotia

REDUPLICATION of parts of the alimentary tract and cysts of entodermal origin are rare but generally known. The best known are reduplications of the small intestine commonly presenting as a blind tube. They are mesenteric in situation and usually open into the small intestine near the cecum. They may be complicated by ulceration and sometimes perforation. Often the reduplication has no communication with the intestine and thus constitutes a variety of mesenteric cyst. Small duodenal diverticula are common but the majority are not of strict embryonal origin being pulsion, or false, diverticula associated with imperfection of the musculature and other local conditions. Other small bowel diverticula are usually explained by reference to abnormal canalization of an original solid tube in embryonic development. Occasionally a mediastinal cyst is encountered where the wall is a replica of the stomach including mucosa and musculature. This is considered to represent an early sequestration in the development of the foregut. Instances of reduplication of the stomach are also known but are very rare. They are generally encountered as varying degrees of bilocularity in situ.

The purpose of this communication is to describe a congenital anomaly in which there was a distinctly separate accessory stomach which was partially intrathoracic. Only 4 similar anomalies have been published as clinical studies.

CLINICAL HISTORY

The patient, a male infant and a firstborn, became irritable at 4 months and could not take solid foods. The infant was admitted to the Halifax Children's Hospital in February 1952 at the age of 8 months in a poor nutritional state, with marked pallor, irritability, and profuse perspiration confined to the head and neck. There was fever, cough, dyspnea, and cyanosis. Physical examination revealed harsh bronchial breathing and expiratory rales over the left chest posteriorly. Roentgenologic investigation revealed infiltration of the left base of the lung. There was a severe normochromic anemia (hemoglobin 6.6 gm. per cent, packed cell volume 25 per cent) and a leucocytosis (26,000 c./mm. with 62 per cent neutrophil polymorphs). The stools were dark and tarry with altered blood. Trypsin was identified in the stool.

Investigation, including roentgenologic examination of the upper gastrointestinal tract and examination for a hemorrhagic diathesis, was negative and the site and nature of the alimentary bleeding could not be identified. A provisional diagnosis of alimentary telangiectasia or duodenal ulcer was made, and it was decided to combat what was thought to be a complicating respiratory infection and to raise the nutritional state. A course of aureomycin and whole blood transfusions (total 600 c.c.) was given. There was marked general improvement. The blood in the stools disappeared but the infiltration in the lung did not clear up completely. The patient was discharged after 4 weeks of hospitalization but was still kept under aureomycin treatment.

Three weeks later, April 2, the infant was admitted in shock due to blood loss from gross melena. After resuscitation a series of x-ray studies of the alimentary tract did not reveal any abnormality except duodenal spasm. The melena continued and laparotomy was performed on April 29. A mass was found surrounding the first and second parts of the duodenum which was covered by adhesions. A diagnosis of duodenal perforation into the lesser sac was made and the abdomen was

From the Institute of Pathology, Government of Nova Scotia, and Department of Anatomy, Dalhousie University, Halifax, Nova Scotia.

Fig. 1.

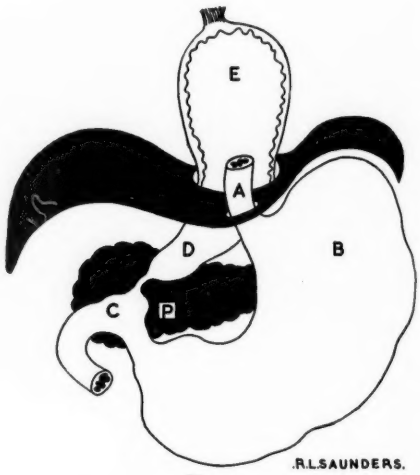

Fig. 2.

Figs. 1 and 2. Photograph and diagram of specimen showing: *A*, the esophagus, *B*, stomach, *C*, first part of the duodenum, *D* and *E*, accessory stomach with *E* intrathoracic, *P*, pancreas. In Figure 1 only a small part of *D* can be seen and the esophagus, cut away, is marked in white. Compare Figures 1 and 2.

closed. Antibiotic treatment was continued and the melena stopped 1 week postoperatively.

During this time, abnormality in the chest persisted and was considered to represent an abscess. The findings will be discussed after the autopsy description. The patient was discharged June 13 in good clinical condition although roentgenologic abnormality was still demonstrable in the chest.

The patient was admitted to hospital in shock on July 6 and died a few hours later.

AUTOPSY EXAMINATION

Since a gross and confusing abnormality of the alimentary tract was discovered on opening the thorax and abdomen, the alimentary tract with the liver and pancreas was dissected as a block and the lumen from the terminal esophagus to the jejunum was stuffed with pledgets of cotton wool soaked in formalin and inserted through small incisions. The specimen was examined later after fixation (Figs. 1 and 2). The esophagus (*A*) and its diaphragmatic hiatus were normal. The stomach (*B*) appeared normal apart from complete loss of the rugose pattern of the mucosa of the body. The first part (*C*) and the proximal half of the second part of the duodenum were surrounded by an annular pancreas. Beyond this the second part of the duodenum on its anterior aspect was autolytic and perforated. There was surrounding inflammatory reaction and light adhesions. No doubt this was a site of ulceration and hemorrhage during the patient's illness, the appearances being complicated by agonal or postmortem changes. The first part of the duodenum embraced by the annular pancreas was slightly expanded and on its superior aspect funnelled into a small channel which would only admit a probe 2 millimeters in diameter. On following this channel upward it opened into a tube-like structure (*D*) which ran for almost 5 centimeters to a hiatus in the diaphragm from where it expanded into a muscular intrathoracic pouch (*E*) lined by mucosa. At the autopsy the pouch was collapsed but when stuffed measured 7 centimeters in diameter. The pouch (*E*) lay on the left side of the thorax behind the heart. Examination of the wall of the pouch (*D–E*) showed a musculature and mucosa of stomach type, and in addition, the musculature was hypertrophied as compared with the normal stomach. Examination of the remainder of the intestine showed altered

ood in the lumen but no ulceration or other normality.

The left pleural cavity, in addition to containing the accessory stomach, was filled with a dark brown liquid, and the left lung was completely collapsed. Since the fluid was obviously gastric juice containing altered blood a search was made for a perforation in the thoracic stomach. Inspection revealed no definite ulceration of the mucosa but there were dense fibrous adhesions around the thoracic aspect of the diaphragmatic hiatus. It was presumed that there had been an acute perforation in this site which had healed on escape of the gastric juice. Fibrous adhesions were also marked on the posterior aspect of the thoracic pouch where they blended firmly with the integument of the vertebrae.

We can conclude that there was a large accessory stomach, partially intrathoracic, which communicated with the duodenum by a narrow channel invested by an annular pancreas. From the history it is evident that there was ulceration with hemorrhage from this abnormal system. One site was the second part of the duodenum which was found autolytic, perforated, and surrounded by adhesions. It is obvious too from the roentgenologic examination that the accessory stomach became distended with gastric juice and emptied from time to time. Furthermore, there had been ulceration and inflammation of the thoracic stomach, with at sometime, an acute perforation leading to collapse of the left lung which occurred near the diaphragmatic hiatus but had been sealed off by inflammatory adhesions.

We have already noted that fibrous tissue was dense posteriorly over the integument of the thoracic pouch and was reflected over the vertebrae. In the embryologic discussion special emphasis will be put on this as a preexisting congenital anomaly. Histologic examination was equivocal since inflammatory reaction was present in the tissue.

ROENTGENOLOGIC EXAMINATION

The roentgenologic findings are explained in the light of the pathologic findings. On the first examination the thoracic stomach was collapsed and hidden behind the heart, only showing as an elliptic density. On the second admission the thoracic stomach had expanded to fill two-thirds of the thorax and had a fluid level (Fig. 3).

Fig. 3. The dark radiolucent shadow of the diverticulum is seen above and medial to the gas in the stomach fundus. The vertebral cleft and halves (hemivertebrae) of the sixth cervical are also seen.

DISCUSSION

Only 4 cases of the anomaly which we described have been published, 1 case from Holland by van der Hal and Mooy, and 3 cases from Boston by Gross, Neuhauser, and Longino. They have been designated as macrodiverticula in the literature rather than as accessory stomachs. The Boston cases were diagnosed during life and cured by operation. Our case differs from the others in that it is the only instance of a patient with an annular pancreas and the only one with the thoracic part of the accessory stomach on the left side; the others were all on the right. Again only 1 other patient had the tiny communication with the duodenum. The lining of the diverticula has been gastric except in 1 case in which it was intestinal.

All cases have followed the same clinical and roentgenologic pattern. They have been encountered in infants with 1 exception, that of a 4 year old child. The presenting symptoms

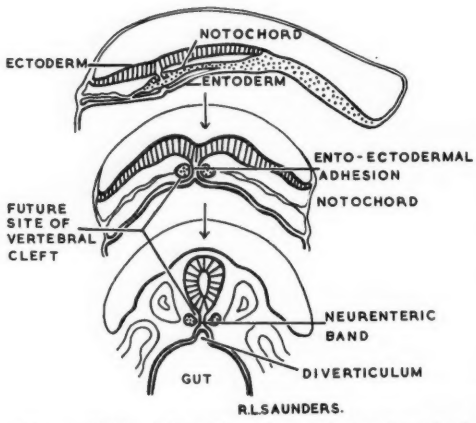

Fig. 4. Mode of formation of an ento-ectodermal adhesion and its differentiation into a "neurenteric" band. Such bands may elongate and give rise to traction diverticula, cysts, or strands.

have either been due to distention with gastric juice after a meal, when pressure led to respiratory embarrassment and cyanosis, or have been associated with ulceration of the mucosa in the anomaly. This produces either gross melena or an inflammatory reaction. Our patient had all of the complications mentioned although cyanosis was not marked except terminally and was associated with collapse of the left lung. There was intermittent respiratory embarrassment as well as episodes of severe melena. Finally, there had been actual escape of gastric juice into the pleural cavity while dense adhesions indicated inflammatory reaction of longer standing. The inflammation and hemorrhage resulted from erosions associated with pressure of the confined juice and from the fact that the excessive amount of gastric juice was largely, as the Boston workers describe, unneutralized. In the Dutch case there was a classical peptic ulcer at the junction of the anomaly with the duodenum. In our case there was no definite chronic ulceration. Roentgenologic examination gives the key to the diagnosis—an intrathoracic cyst which varies in size and often exhibits a fluid level (Fig. 3). The Boston workers discuss surgical procedures in detail.

The usual embryologic explanation of congenital alimentary reduplications is represented as an anomaly of the canalization of an original solid tube but this does not suffice to cover the extent of the anomaly described. One of us (R. L. S.) is responsible for the following discussion.

The fact that this large diverticulum or accessory stomach extended upward through the diaphragm and was connected to the vertebral column suggested a similarity to the alimentary diverticula and "neurenteric" strands noted in association with spinal deformities of the combined spina bifida type.

Anterior and posterior or combined spina bifida manifests itself as a vertebral cleft or diastema of greater or lesser degree, flanked by partially fused or widely separated vertebral halves or hemivertebrae. Such a vertebral cleft may be connected with, or even transmit, some part of the alimentary tract. In a survey of 37 such cases Saunders noted that a diverticulum or strand (Fig. 5) often passed from some part of the alimentary tract (e.g., esophagus, stomach, or small intestine) toward the vertebral cleft and spinal cord, hence the term "neurenteric" diverticulum or strand was used to describe such connections. Embryologically the vertebral cleft and "neurenteric" connections were accredited to the formation (during the presomite phase of embryonic development) to a cleft notochord, and an ento-ectodermal adhesion that connected the developing gut with the neural tube. This theory has received support from Shoul and Ritvo, as well as Patten's recent demonstration of anomalous fusion of notochord to neural tube in a human embryo.

The roentgenograms of this case accordingly were enlarged and examined carefully for evidence of vertebral anomalies. This revealed a typical vertebral body cleft of the sixth cervical vertebra. In short there were two imperfectly fused vertebral body halves (hemivertebrae) such as represent a minor degree of vertebral cleft (Fig. 3). This finding led to a study of the histories and roentgenograms accompanying case reports of other examples of accessory stomach or gastric diverticula (duplication), and also of certain intrathoracic diverticula and cysts of intestinal origin, for evidence of concomitant congenital anomalies of the spine.

Gross, Neuhauser, and Longino mentioned at 2 of their 3 cases of thoracic diverticula ginating from the intestine were accompa- d by developmental anomalies of the cervi- and upper thoracic vertebrae. One was ted to show a Klippel-Feil type of spinal omaly, but examination of the roentgeno- aphic reproduction suggests that it was lly a combined spina bifida. This is not rprising since it is not generally recognized at the essential identity of the Klippel-Feil omaly is that of a variant of combined an- rior and posterior spina bifida; mention of is will be made later. Two of these thoracic verticula described by Gross, it is interesting note, possessed a lining mucosa of gastric pe, whereas the third was of jejunal type. Further evidence that such diverticula, th gastric and intestinal frequently arise out and are associated with, maldevelopment the vertebral column, may be had on ex- ining the cases grouped by Saunders under e heading (group 4, subgroup A) of examples combined spina bifida which show a verte- al cleft-traversing strand or diverticulum nnecting the alimentary tract and spinal ord. Such cases are those of Budde, Bell, and eller and Sternberg.

Budde's case is particularly interesting. A baby girl, aged 1 year and 9 months who possessed a cervical malformation (kurzhals or short neck), at autopsy showed a cleft of the third and fourth vertebral bodies. Removal of the cervical and thoracic organs revealed in the midline a rounded strand 3 millimeters in diameter and 15 centimeters in length. This descended from the vertebral cleft through the posterior mediastinum where it lay between the esophagus and spine. It then passed through the esophageal opening of the diaphragm and terminated in a gastric diverticulum arising from the greater curvature of the stomach. Histologic section of the cervical column showed that the strand passed through the vertebral cleft and communicated with the spinal cord. In passing it may be noted that a cervical cleft and gastric diverticulum are features common both to this case and the one here presented.

Bell likewise described a case of a male neonatal infant with a cervical type of anterior spina bifida, in which a gastric diverticulum extended upward behind the esophageal opening of the diaphragm (just as in this case) to become attached to a vertebral cleft involving the cervical and upper thoracic vertebral bodies.

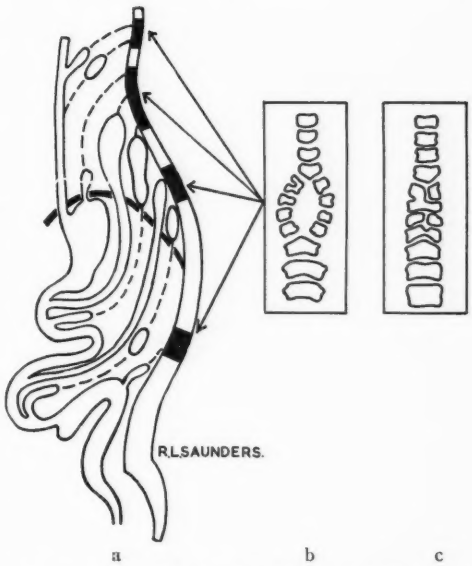

Fig. 5. Diagram based on specimens, case reports, and roentgenograms. a, Shows how an ento-ectodermal adhesion may give rise to traction diverticula, cysts, or "neurenteric" strands involving foregut, midgut, or hindgut derivatives. b, A frank combined spina bifida flanked by hemivertebrae; commonest in cervicothoracic regions. c, Shows the varying fusions and clefts which may arise out of growth transformations of b.

Similarly Feller and Sternberg examined a short-necked neonatal female infant who displayed a gastroesophageal diverticulum that was directed posteriorly and upward toward a cleft involving the cervical and upper thoracic vertebral bodies.

Thus it will be understood that an ento-ectodermal adhesion may not only result in a local disorganization of the vertebral precursors, but give rise to a "neurenteric" band or connection with some part of the alimentary tract (Fig. 4). Such a band may or may not elongate with growth and so interfere with diaphragmatic development. Again it may cause traction diverticula at one or both points of attachment (i.e., alimentary or neural) or

give rise to intrathoracic or intra-abdominal cysts. Thus, it would appear that many so-called "enterogenic" diverticula, cysts, and strands owe their existence to coincident malformation of the embryonic spinal axis, which may or may not later express itself as a frank vertebral body cleft, or some minor degree of combined spina bifida. Support of this contention is provided by a case described by Korff, in which an S-shaped intestinal (ileal) loop occupied a thoracic vertebral body cleft, while an ileal diverticulum was directed toward both it and the vertebral cleft.

It would appear that in some instances an ento-ectodermal adhesion or "neurenteric" connection may become elongated and attenuated during growth. Thus it is likely that a diverticulum so formed may become divided into two, with the resultant formation of a cyst, or cysts, that may lie independent and some distance from the alimentary tract and diverticulum, or adjacent to it and even fused with some proximal part of the alimentary tract (Fig. 5). Hence the case described by Black and Benjamin appears to be of special significance since it exhibited two separate cysts, one intrathoracic and the other intra-abdominal, and both of which showed features of gastric mucosa. The intrathoracic cyst was described as a large retromediastinal enterogenous cyst attached to the anterior aspect of the third to twelfth thoracic vertebrae. The thoracic and abdominal cysts would, in fact, appear to be two separated parts of a gastric diverticulum, resembling the second type described by Gross, Neuhauser, and Longino. Comparison of Figures 3 and 2 of these authors will immediately convey the impression that they depict related variants. Coincident intrathoracic and intra-abdominal cysts, lined however by intestinal mucosa, were discovered by Brass (quoted by Nicholls) in no less than 3 premature infants.

Following on this it is perhaps pertinent to such gastric (and intestinal) diverticula, that Nicholls reported an intrathoracic cyst which was lined by gastric mucosa. On removing same he was charged by the pathologists with having removed part of the stomach. Roentgenograms showed a large cyst lying immediately anterior to the 7 lower thoracic vertebrae, while hemivertebrae (so characteristic of vertebral clefts) are detectable just above the tracheal bifurcation in the region of the fourth thoracic vertebra. This author collected 12 cases of intrathoracic cyst of intestinal type, of which no less than 8 were classified as gastric cysts since their microscopic structure was that of typical gastric mucosa. The remainder had a mucosal structure of either esophageal, gastrointestinal, or small intestine type. The majority were described as retropleural, lying behind the trachea and esophagus, or attached to the posterior mediastinum, thereby leaving little doubt of an intimate vertebral relationship. One of the cases mentioned was that of Staehelin and Burchhardt (quoted by Boss); after operation for spina bifida an intrathoracic gastric cyst was revealed at autopsy.

Mixter and Clifford also described a large cyst of typical gastrointestinal type which lay behind the trachea and esophagus. Part of it was a "thin, fibrous, cystic mass which extended into a cavity which had been formed by the erosion of the bodies of the vertebrae." Since the infant was 7 weeks old it is highly probable that the so-called erosion was in fact a vertebral body cleft of the combined spina bifida type.

Since the case here presented possessed such a narrow communication with the duodenum it may be considered as occupying an intermediate position between the wide mouthed alimentary communication exhibited by Gross's intrathoracic gastric diverticula, and the intrathoracic cysts lined with gastric mucosa as described by Nicholls.

An interesting feature of these thoracic diverticula and cysts connected with the stomach or intestine (e.g., duodenum or jejunum) is that most cause a protrusion of the right side of the mediastinum, or even frankly bulge into the right hemithorax, and consequently are often detectable roentgenologically. This tendency to lie to the right of the vertebral column is probably caused by a dextrolateral displacement of the embryonic "neurenteric" connection by the developmental processes of gastric and gut rotation. In view of the suggested genesis of the condition it is to be expected that some should occupy a median prevertebral position and lie behind

both the trachea and esophagus. Cardiac rotation may conceivably influence such few as but the mediastinum toward the left.

Consequently the detection of either partial or frankly cleft vertebral bodies, with or without interfusion of the hemivertebrae, is indicative of a degree of combined spina bifida. That is to say, there may be a complete or partial anterior and posterior spina bifida involving one or more vertebrae. This condition may involve any region of the vertebral column, but is most frequent in the cervical and thoracic regions, and this is no doubt because the "critical moment" (Stockard) of the notochord coincides with the formation of its cephalic end. As a corollary to its genesis the existence of such a spinal anomaly should suggest the possible coexistence of alimentary and neural anomalies. Thus the presence of gastrointestinal symptoms or signs in the face of roentgenologic demonstration of a vertebral body cleft should bring to mind the possibility of coexisting alimentary diverticula or cysts, let alone the likelihood of neural malformation. It should be noted that a vertebral cleft is not always obvious since growth usually modifies and induces some fusion of the flanking hemivertebrae. Again the apex of the diverticulum does not necessarily coincide with the fixation site as represented by the vertebral defect.

In conclusion it may be mentioned that Saunders is preparing a monograph dealing with the essential identity of the Klippel-Feil type of spinal defect, iniencephaly, and diastematomyelia, since his studies have led him to believe that these anomalies are all related to the basic condition of combined spina bifida. Briefly all are related variants that arise as the result of localized duplication of the notochord, or faulty localized notochordal differentiation, and either of which may or may not be attended by the formation of an ento-ectodermal adhesion, with consequent concomitant formation of neural or alimentary anomalies or both (e.g., duplications, diverticula, and connecting strands).

SUMMARY

The case is described of an infant with feeding difficulty and respiratory embarrassment who developed bouts of severe melena. Roentgenologic examination revealed an intrathoracic cyst on the left side which varied in size and sometimes exhibited a fluid level. Autopsy disclosed a large accessory stomach, partially intrathoracic, which communicated with the first part of the duodenum through a tiny channel which was embraced by an annular pancreas. The gastric anomaly is rare, but can be diagnosed in life because of the unique combination of clinical and roentgenologic findings, and is amenable to surgery. Saunders has shown that such anomalies are often accompanied by spinal anomalies demonstrable by x-ray examination. Particularly the presence of a vertebral body cleft should bring to mind the possibility of coexisting alimentary diverticula or cysts, quite apart from possible neural malformation. The related embryogenesis is discussed in detail.

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PRIMARY RETICULUM CELL SARCOMA OF BONE

Report of 44 Cases

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SINCE the classical description of primary reticulum cell sarcoma of bone by Parker and Jackson in 1939, there have been few reports in the medical literature concerning this rare and somewhat controversial neoplasm. A series of 37 patients with histologically proved reticulum cell sarcoma primary in bone was reported from Memorial Hospital in 1950 by Coley, Higinbotham, and Groesbeck. It is our purpose to present 8 additional cases and to summarize the end-results of the entire series through 1953.

Parker and Jackson's original report comprised 17 patients, 13 from the Bone Sarcoma Registry and 4 of their own. In addition to the Memorial Hospital series reported in 1950, Valls, Musculo, and Schajowicz reported the findings in 7 cases. McCormack, Ivins, Dahlin, and Johnson (4) in 1952 reported 32 patients with primary reticulum cell sarcoma of bone, of which 25 were stated to be unequivocal. This predominantly pathologic study clearly indicates that these tumors are a distinct entity and should be so classified. The authors state that 2 cases in their series were difficult to distinguish histologically from Ewing's sarcoma. Although they do not report concise survival figures, their 5 year survival rate reflects the significantly more favorable prognosis as compared to other forms of bone sarcoma, and indeed, to generalized reticulum cell sarcoma and Ewing's sarcoma in particular. Ivins and Dahlin (3) analyzed the Mayo Clinic series of 49 cases in 1953, which included the previously reported patients of McCormack, Ivins, Dahlin, and Johnson (4). These authors again present excellent clinical and pathologic evidence that primary reticulum cell sarcoma of bone is a distinct entity as opposed to generalized reticulum cell sarcoma, Ewing's sarcoma, and metastatic neuroblastoma. They recommend amputation, irradiation and Coley's toxins in the definitive treatment of the primary lesion, and present a 5 year survival rate of 35.7 per cent in 10 patients with solitary lesions on admission. Of 10 patients with multiple lesions on admission, they report 8 to be dead of whom 3 lived 3 or more years. Strange has recently reported 3 instances of reticulum cell sarcoma which were primary in the skull—the first report of primary involvement of this bone.

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MEMORIAL HOSPITAL SERIES

Our criteria for inclusion of a case as primary reticulum cell sarcoma of bone were defined in a previous communication (1). They are as follows: (1) clinically a primary focus in a single bone on admission; (2) unequivocal histologic proof from the bone lesion (not from a metastasis); (3) metastases present on admission only if regional, or if the onset of symptoms of the primary tumor preceded the appearance of the metastases by at least 6 months.

The clinical, roentgenologic, and histologic features of this disease have been presented in detail elsewhere (1, 6), and will not be enlarged upon in this report except in review, as all new patients presented similar clinical findings.

Since 1925, forty-four patients fulfilling these criteria as primary reticulum cell sarcoma of bone have been treated at this institution. In 1950, thirty-seven of these were described, and through 1953 eight new cases have been treated (Table I). Since the previous report, 1 patient of the original series (Case 26) has died. The autopsy diagnosis was Ewing's sarcoma, although at the time of report, the pathologic diagnosis was reticulum

TABLE I

C...	No. ... e	Bone	Treatment			Tumor dose of irradiation, roentgens	Results			Remarks
			Surgery	Toxins	Irradiation		Well, mos.	Died, mos.	LWD, mos.	
		Humerus	—	3 courses	X-ray	3134	—	—	40	See case report
		Ilium	—	1 course	X-ray	2840 4068	—	5	—	4 years' duration before admission
		Ilium	—	1 course	X-ray	3771	—	9	—	Generalized metastases 5 mos. after administration
		Femur	—	1 course	X-ray	3580	—	2	—	—
		Scapula	—	2 courses	X-ray	3090	22	—	—	—
		Femur	Amputation	1 course	—	—	—	7	—	Lung metastases 3 mos. postoperative
		Humerus	Amputation	—	X-ray Preop.	8010	—	29	—	Biopsy interpreted as osteogenic sarcoma originally
		Femur	—	2 courses	X-ray	3000 2400	—	—	1	Inguinal node adenopathy 4 mos. after therapy to femur. No recurrence in femur

cell sarcoma; accordingly, this case has been deleted from the series. The foregoing serves to emphasize the close histologic similarity of reticulum cell sarcoma to Ewing's sarcoma; in fact, occasionally the distinction cannot be made with certainty. Recently, it has been suggested to us that glycogen stains might be of aid in the differential histologic diagnosis of these two conditions. The cells of reticulum cell sarcoma are reported to stain negatively for glycogen. However, we have had no experience with this technique.

This paper will deal only with pertinent findings as they are related to the series follow-up and the 8 new patients.

Age. The age of the 44 patients ranged from 11 to 67 years, with an average of 34 years. The age distribution according to decade represents no significant change from that previously reported: in the first decade, no cases; 14 in the second decade; 7 in the third decade; 6 in the fourth decade; 7 in the fifth decade; 8 in the sixth decade; and 2 in the seventh decade.

Sex. There were 32 males and 12 females, a ratio of over 2.1 in favor of the male. This preponderance in the male has been previously noted.

Bones involved (*Table II*). The incidence of the disease in the long bones of the extremities as compared to the bones of the trunk is 2:1. This fact we regard as significant since Craver and Copeland found the opposite relationship to be present in the bone involvement of generalized reticulum cell sarcoma in their series of cases.

Etiology. The etiology is unknown. The relationship to trauma has been discussed at length (1). Suffice it to say, if trauma plays any role it probably serves to call the patient's attention to a tumor which is already present.

TABLE II.—BONE INVOLVED (44 CASES)

	No. of cases
Long bones	
Tibia	9
Femur	11
Fibula	2
Ulna	2
Humerus	5
Total	29
Flat bones	
Rib	2
Sternum	2
Scapula	4
Ilium	5
Vertebra	2
Total	15

Ratio 2:1

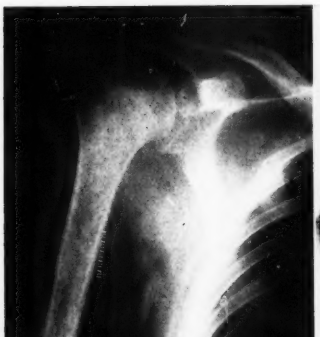

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1. Roentgenogram of primary lesion on admission.
Fig. 2. Photograph of patient prior to treatment on second admission (Case 37).

Fig. 3. Photograph of patient taken 1 year and 11 months after treatment of metastases with injections of toxins alone.

Pathology. There is general agreement that the cell of origin is the reticulum cell, and that the histologic appearance is indistinguishable from the generalized form of the disease. The gross and microscopic characteristics have been extensively reviewed in several excellent studies. It should be re-emphasized that the histologic differentiation from Ewing's sarcoma and metastatic neuroblastoma may be extremely difficult.

Symptomatology and physical findings. The 8 new cases have conformed to those reported in the previous communication. Pain has been the most significant initial complaint and was noted by all 8 patients. A high percentage demonstrate a palpable mass or soft tissue swelling. Of particular interest and of diagnostic importance is the apparent good health of the patient when compared to the frequently extensive nature of the disease process. This is in contrast to the less satisfactory general condition of patients first seen with Ewing's sarcoma or metastatic neuroblastoma. Tenderness, local heat, and temperature are noted less often in that order of frequency.

Analysis of new patients. Of 8 cases only 1 has been without evidence of disease since definitive therapy. Case 43 was originally diagnosed histologically as osteogenic sarcoma with involvement of the right humerus, on the basis of a biopsy performed elsewhere. He was treated with massive preoperative irradiation, and an interscapulothoracic amputation was performed. Metastasis developed in the ilium and rapid generalization of the disease thereafter. Review of the original microscopic sections has confirmed the diagnosis of reticulum cell sarcoma, the first manifestation of which was located in the humerus. The patient died 2 years and 5 months following the initial therapy. This case represents again the difficulties encountered in the histologic diagnosis. The disease in another patient (Case 37) was intriguing from several points of view; it is presented in detail.

CASE 37. E.P., a 48 year old white male truck driver, was first admitted to Memorial Hospital on June 13, 1950 complaining of gradually increasing pain and swelling of the right upper arm for 2 months. Six months previously he had received an accidental blow to the same area, followed by moderate pain and swelling which disappeared in 6 to 8 days. The remainder of the history was not contributory. Examination revealed the right arm, forearm, and hand to be edematous and warmer than the left. Motion of the right shoulder was limited by pain to 30 degrees of passive abduction. Otherwise, the examination was entirely negative and the patient looked to be in excellent health. X-ray films on admission (Fig. 1) revealed a large area of destruction

in the shaft of the proximal right humerus, with some reactive bone formation. The cortex was destroyed along the lateral aspect. Evidence of a soft tissue mass was noted medially. The chest film was completely negative. An aspiration biopsy of the right humeral lesion was attempted on admission but was not successful. Accordingly, an open biopsy was performed, and the histologic diagnosis was reticulum cell sarcoma of the right humerus invading the surrounding soft tissue. From June 27, 1950 to July 18, 1950 the patient received irradiation to the right humerus delivered through one anterior and one posterior portal, measuring 35 by 15 centimeters, and also including the right supraclavicular region with the 1,000 kilovolt machine. The tumor dose totaled 3,134 roentgens. In addition, from June 28, 1950 to July 11, 1950 he received 13 daily injections of Coley's toxins. On discharge there was a considerably increased range of shoulder motion. There was no pain, tenderness, edema, or increased temperature of the extremity. Thereafter, the patient was followed in the clinic with no evidence of recurrence and presenting a steadily increasing range of right shoulder motion.

He was readmitted to Memorial Hospital on May 11, 1951 (Fig. 2) complaining of a "crooked mouth," tearing of the right eye, and drooping of the right lower lip of 4 weeks' duration. Examination revealed extensive right periorbital edema, weakness of the right upper eyelid, and weakness of the musculature of the mouth. Large soft tissue masses were noted in each temporal region, which were firm, diffuse, and nontender. A small nodule in the left frontal area of the scalp was firm, fixed, and not tender. The right external auditory meatus was occluded by edema. With the exception of 1 small right axillary node, no adenopathy was detected. An aspiration biopsy of one of the temporal masses was not revealing. Thus, an open biopsy was carried out, which revealed the tumor tissue to be limited to the soft tissue. The pathologic report was tissue "consistent with malignant lymphoma." Roentgenograms of the skull on May 12, 1951 revealed an area of radiolucence 8 millimeters in diameter in the posterior aspect of the skull. No other bony lesions or evidence of metastasis could be detected. X-ray films of the right humerus revealed progressive healing and no evidence of recurrence. The chest film was negative. The patient was treated with Coley's toxins administered daily from May 14, 1951 to May 28, 1951 to a total of 15 injections. By the ninth day marked regression of the temporal lesions had occurred, and on discharge no masses, weakness, or adenopathy could be detected. A prophylactic course of 12 injections of Coley's toxins was administered between July 4, 1952 and July 16, 1952, although the patient had been free of any evidence of disease.

Since that time he has been followed at frequent intervals in the bone tumor clinic, with no evidence of recurrent disease. When last examined, 2 years and 5 months since recurrence, the patient was free of detectable disease. A full range of painless motion was present in the right shoulder, and he has been fully employed driving his truck without difficulty (Fig. 3).

TABLE III.—FIVE YEAR END-RESULTS
(1925 TO 1948)

		No. of cases
Total number of patients		32
Indeterminate group (lost to follow-up without evidence of disease less than 5 years)		1
Determinate group		31
Failures		
Dead as result of reticulum cell sarcoma	13	
Lost to follow-up with disease	0	
Living with recurrence	3	
Total number of failures in treatment		16
Successful results		
Free from disease after 5 years or more		15
		(48.4 per cent)

A dramatic response to 1 course of Coley's toxins was noted also in Case 1 which has been fully documented in the literature (1). That patient is now well and without disease for a period of 27½ years. Isolated instances such as these lead us to believe that the toxins may be of value in this disease—a conclusion also reached by the Mayo Clinic group (3). They report a 29 year survival treated with toxins alone for a lesion in the femur.

FOLLOW-UP

Since the previous communication 1 patient (Case 13) who was without evidence of disease for 10 years, has succumbed with generalized metastases 10 years and 11 months after treatment. Another patient (Case 15) was free of disease 8 years and 6 months, and then died of generalized metastases. One patient (Case 23) was without evidence of disease for 5 years and 6 months and then developed metastases which required bowel resection. She

TABLE IV.—TEN YEAR END-RESULTS
(1925-1943)

		No. of cases
Total number of patients		20
Indeterminate group (lost to follow-up without evidence of disease more than 5 years but less than 10 years)		2
Determinate group		18
Failures		
Dead as a result of reticulum cell sarcoma.	12	
Lost to follow-up with disease	0	
Living with recurrence	0	
Total number of failures in treatment		12
Successful results		
Free from disease after 10 years or more		6
		(33.3 per cent)

is now clinically well 6 years and 5 months following definitive therapy, and 1 year since recurrence. Another patient (Case 34) was without disease for 1 year and 1 month; generalized metastases occurred and the patient died 1 year and 5 months following treatment. Another patient (Case 35) was under treatment with metastases at the last report and died 3 months following admission.

The fact that metastases occurred in 2 patients, who had been well for 10 and 8 years respectively following treatment, indicates that a 5 year survival rate without disease is much less reliable in this tumor than it is in certain other forms of bone sarcoma.

TREATMENT

Parker and Jackson stated that they could not advise the best treatment. However, it was their feeling that amputation and postoperative irradiation would produce the best results. In the previous study from Memorial Hospital (1) amputation was not found to be the treatment of preference. The predominantly pathologic study of McCormack, Ivins, Dahlin, and Johnson (4) revealed that amputation plus irradiation had been used in the majority of their cases. In 1953 Valls, Musculo, and Schajowicz were of the opinion that recurrence was relatively frequent following irradiation, despite the radiosensitivity of the tumor. Because of this they advised wide local excision. Ivins and Dahlin (3) recommend amputation or radical excision in addition to postoperative irradiation locally and to the regional nodes.

The treatment in the 8 new cases of the present series is presented in Table I. In all cases with the exception of Cases 42 and 43, irradiation was given plus one or more courses of Coley's toxins. The patient in Case 43 was operated upon under a mistaken diagnosis. Of these 8 patients, 5 died of disease, 2 of whom were subjected to amputation. Two patients (Cases 37 and 44) are classified as living with disease. At this time, however, these patients are clinically well and gainfully employed. One patient (Case 41) is free of evidence of disease 1 year and 1 month after definitive therapy for a primary scapular lesion.

The 5 and 10 year end results are presented in Tables III and IV. The 5 year survival without evidence of disease is 48.4 per cent. This is compared to 47.6 per cent in 1950 (I). Thus, the 5 year survival without disease has not changed appreciably in the past 4 years. The 10 year survival without evidence of disease has fallen to 33.3 per cent as compared to 38.5 per cent. We believe that this is a very significant finding, in that recurrence or rapid metastases may occur after 5 years of apparent freedom from disease. To be sure this is not the general rule; however, we do advise that these patients should be examined frequently for many years after the definitive treatment and appropriate measures instituted immediately in the event of any untoward symptoms, particularly pain.

From the data presented it is our conclusion that the most efficacious therapy is irradiation of the primary lesion in addition to one or more courses of Coley's toxins, and that amputation is definitely not indicated except in the treatment of complications which might possibly arise.

SUMMARY

1. Forty-four cases of primary reticulum cell sarcoma of bone are presented.

2. Eight new cases have been added to the original series.

3. Follow-up data on the group as a whole are analyzed.

4. Five and 10 year survival statistics are reported for the entire series through 1953.

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ADMINISTRATION OF DEXTRAN BY HYPODERMOCLYSIS

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REPORTS by Grant and associates and Schwartzman indicate that plasma may be given rapidly by clysis provided hyaluronidase is used. These investigators believe that the injected plasma gets into the blood stream by way of the lymph. More recently, Narat, Casella, and Cangelosi have reported studies involving rats, rabbits, and dogs in which they believed that dextran and polyvinylpyroliodone might be given intraperitoneally to combat various states of shock. Dextran, because of its ease of manufacture, stability on storage, and lack of danger in causing hepatitis, has been suggested as the plasma expander to be used in case of major disaster. In such an event, it would be of advantage to be able to administer the material intraperitoneally or by hypodermoclysis, but before this can be done information must be obtained on the rate of entrance of the administered dextran into the blood. In view of the reports of others, an investigation was undertaken to determine whether dextran would be effective when given extravascularly, since it has been shown earlier that the rate of absorption of fluid given intraperitoneally, or by hypodermoclysis, is slow and may cause a diminution in plasma volume prior to its absorption.

METHODS

After ether anesthesia, 40 rats were weighed. A microhematocrit determination was then done, using the Guest-Weichselbaum centrifuge on tail vein blood. Each animal was then given intraperitoneally 0.1 milliliter of a 6 per cent dextran solution in 0.9 per cent saline per gram of body weight. Alternate animals were given 0.55 TR (turbidity-reducing) unit of hyaluronidase per milliliter of dextran solution. At hourly intervals, for the first 6 hours after the instillation of the dextran, and periodically thereafter for the next 8 hours, the animals were reanesthetized and the hematocrit determinations repeated. At this time, the peritoneal cavity was opened and the amount of fluid present measured. The technique employed has been reported earlier by Foreman, Webb, and Schechter and their associates. The volume of the peritoneal fluid recovered was expressed as per cent of dextran solution administered, and the serial hematocrit was also expressed as per cent of the control value. Samples of the peritoneal fluid were analyzed for dextran.

Four fasting human male subjects, who showed no fluid or electrolyte derangement, were given 1,000 milliliters of dextran in 0.9 per cent saline by hypodermoclysis. In 2 of the men, 150 TR units of hyaluronidase were added to the dextran injected into the lateral aspects of the thighs. Plasma volumes were determined before and 4 hours after the hypodermoclysis of dextran, using radioactive iodinated human albumin. Blood pressures and hematocrits were measured at half hour intervals during this period. The dextran content of the blood was determined 4 hours after completion of the clysis.

RESULTS

The effect of dextran, when given intraperitoneally to the rat, on the hematocrit and on the amount of fluid recovered from the abdomen is summarized in Figures 1 and 2. In these experiments there appears to be little or no difference in the hematocrit changes and the amount of fluid recovered from the abdomen which could be related to the hyaluronidase given. Table I shows the amount of dextran found in the peritoneal fluid of the rats at various times after instillation. The values in the table are expressed in three ways:

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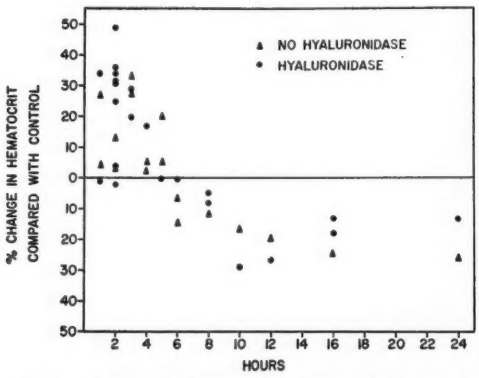

Fig. 1. Changes in hematocrit following the intraperitoneal injection of a solution of 6 per cent dextran in 0.9 per cent sodium chloride. The hematocrit is expressed as per cent of the control value which was obtained from each animal, immediately before the study was begun.

first, the grams of dextran per 100 milliliters of peritoneal fluid; second, as total amount of dextran found in the fluid; and, lastly, as the percentage of the administered polysaccharide which was recovered at the specified time intervals. Those animals which did not receive the hyaluronidase still had 56 per cent of the original amount of dextran in their peritoneal fluid 6 hours after it was injected. This would indicate that the material is slowly absorbed. The results obtained from the animals receiving the hyaluronidase is a little more variable but still indicated that

TABLE I.—DEXTRAN IN PERITONEAL FLUID OF RATS

	No hyaluronidase			Hyaluronidase		
Time after injection, hrs.	gm./100 ml.	Total amount recovered, gm.	Per cent of administered dose recovered	gm./100 ml.	Total amount recovered, gm.	Per cent of administered dose recovered
2	5.7*	1.33	91.0	5.75	1.51	91.5
3	6.0	1.73	96.0	5.93	1.92	92.8
4	5.7	1.31	89.0	4.80	1.50	70.5
5	5.5	1.76	78.5	4.25	1.65	38.1
6	5.2	1.09	56.0			
8	4.7	0.20	11.8			
16	4.4	0.13	5.2	3.5	0.40	21.8

*Each value represents results of duplicate determinations on the peritoneal fluid obtained from individual animals.

the polysaccharide, when given intraperitoneally does not get into the blood stream rapidly. By considering the dextran content of the peritoneal fluid calculated as grams per 100 milliliters of fluid (a level of 6 gm. per 100 ml. was injected) it is evident that the dextran was being absorbed faster than water because both the amount of fluid recovered from the peritoneal cavity and the dextran concentration was diminishing with time. The initially accelerated absorption of dextran from the peritoneal cavity might be explained by the early diffusion of the low molecular weight fractions.

The results obtained from the 4 male subjects are summarized in Table II. Since there was little change in the plasma volume of 3 of the patients 4 hours after the clysis with dextran (because of technical difficulties it was not possible to obtain a postinfusion plasma volume in the fourth patient), it was assumed that the plasma volume was not effectively expanded during this period, probably because only small amounts of dextran entered and remained in the blood stream. The latter assumption was confirmed by the plasma dextran levels obtained at the same time as the second plasma volume was determined. The dextran level of the blood of the 2 patients who did not receive the hyaluronidase was 37.5 and 45.0 milligrams per 100 milliliters, while those who were given the enzyme showed blood dextran levels of 55 and 92 milligrams per 100 milliliters. There were no consistent changes in pulse rate or blood pressure following the infusion. However, a slight increase in hematocrit was noted in the 3 patients studied 4 hours following the dextran clysis. This occurred in both groups of patients.

DISCUSSION

According to reports in the literature plasma may be absorbed at rates comparable to nonprotein solutions when given by clysis, providing hyaluronidase is present. It has been found in rats with thermal burns that the giving of plasma by clysis, with or without hyaluronidase, causes an aggravation of the shock state by reducing the circulating plasma volume. The hemoconcentration found in the

present studies, when rats were given dextran intraperitoneally with or without hyaluronidase, was interpreted as indicating a diminution in plasma volume. Also the appearance of these animals resembles that of those animals used in earlier studies in which large extracellular fluid volume deficits were noted. Ruffled fur and slight cyanosis was noted in the animals employed in the present studies and in our previous work (3) when a plasma hypovolemia existed. In the present study and in the former work when hemoconcentration existed, only small amounts of thick dark blood could be obtained from the cut tail vein, while under control conditions a copious flow of bright red blood could be easily obtained from a similar incision. Since the animals were exhibiting hemoconcentration and evidences of a diminished plasma volume in 2 to 8 hours after the onset of the experiment and the amount of peritoneal dextran containing fluid was diminishing, one must assume that an intracellular shift of fluid had occurred. Attempts to prove that such was the case were made by comparing the water content of the muscle of normal rats and of the animals sacrificed 2, 4, 6, and 8 hours after the intraperitoneal injection of dextran. While too few observations were made to draw positive conclusions, the studies indicated an apparent increase in intracellular fluid. It should be noted that rats used in the present investigation were receiving relatively large doses of dextran (100 ml. per kgm.), as compared with the patients. The data in the present work are not in agreement with those reported by Narat and associates. These latter investigators found that about 80 per cent of the dextran injected into rats was absorbed in 6 hours and as much as 45 per cent in 2 hours. In our work, the absorption was much less per unit of time with only about 10 per cent being absorbed in 2 hours, though the dose of dextran given was 1½ times that used by Narat and his associates.

In patients, we found that the dextran content of the blood reached a level of 37 to 92 milligrams per 100 milliliters 4 hours after the material was given by clysis. Hammerstein and associates reported that 1 hour after the intravenous infusion of 1,000 milliliters of

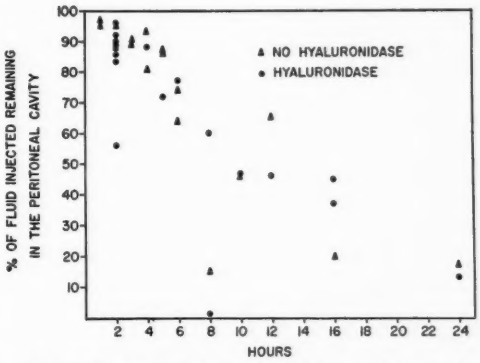

Fig. 2. Per cent of the injected fluid remaining in the peritoneal cavity at various time intervals after administering the dextran solution. Each point represents data from an individual animal.

dextran to normal individuals the blood level was 1,072 milligrams per 100 milliliters and 6 hours later, the level fell to 684 milligrams per 100 milliliters. The dextran levels found in our patients, who received the polysaccharide by hypodermoclysis, was in the range that Bloom and Willcox found 72 hours after giving 500 milliliters of dextran intravenously. Dotti and Pyles reported that in the case of the rabbit, hyaluronidase has the greatest influ-

TABLE II.—RESPONSE TO ADMINISTRATION OF 1,000 MILLILITERS OF 6 PER CENT DEXTRAN IN 0.9 PER CENT SALINE TO 4 NORMAL MALES

	No hyaluronidase		Hyaluronidase	
	W.D.	F.P.	J.H.	M.C
Weight, kgm.	61.3	58.8	65.2	54.5
Plasma volume Control	3249	2765	3264	2698
4 hours	3141	2852	3277	
Hematocrit Control	41.9	45.8	43	45
4 hours	43.5	47.4	46.8	
Four hour plasma dextran mgm./100 ml.	37.5	45	55	92
Pulse Control	76	92	68	112
4 hours	60	80	—	112
Blood pressure Control	120/76	120/70	120/76	140/89
4 hours	116/68	116/60*	106/60	170/88*

*Two hours after the injection.

ence on the blood dextran levels 24 hours after clysis. In the latter report, the blood level of dextran was found to be 277 milligrams per 100 milliliters for the animals who did not receive the hyaluronidase, and 515 for those who did. No other data were given concerning the possibility of an earlier hemoconcentration in these animals. From the present work it appears that dextran given by clysis would not get into the blood stream fast enough to be of clinical value in combating the hypotensive state resulting from a diminished plasma volume. Narat and associates suggested that intraperitoneal infusion of dextran might be of value in treating hemorrhagic shock, imminent shock (such as would occur following crush injuries), or in burns, but because of our findings in both man and rats, we believe the results indicate that the colloid does not enter the vascular tree fast enough to negate the possible danger arising from decreased blood volume and the resulting hypotension. Although it was suggested that the use of "blood volume replenishers" intraperitoneally might also be used in patients exhibiting "chronic shock," it would seem unwise to do so since those states are a result of malnutrition. Such a condition can be more effectively treated by providing an adequate nutritional intake, orally or parenterally, and giving whole blood to correct the diminished red cell mass and deficient plasma volume. No evidence was found in the normal human subjects to indicate that following a hypodermoclysis of 1,000 milliliters of dextran in 0.9 per cent saline, with or without hyaluronidase, any expansion of the plasma volume occurred.

SUMMARY

1. The administration of dextran in 0.9 per cent saline to rats intraperitoneally (100 ml. per kgm.) causes some degree of hemoconcentration in the first 4 hours after administration, which indicates that a decrease in the plasma volume, rather then increase, occurred. The effect is similar whether hyaluronidase is given or not.

2. In 4 human subjects, the administration of 1,000 milliliters of 6 per cent dextran in 0.9 per cent saline by clysis did not cause an increase in the plasma volume, pulse, or blood pressure 4 hours after the material was given. There was a slight increase in the hematocrit in all of the patients. These changes were not influenced by the presence or absence of hyaluronidase.

3. Four hours after the administration of dextran to man by clysis, with or without hyaluronidase, only small amounts were found in the blood stream, 37.5 to 92 milligrams per 100 milliliters. This suggests that the administration of dextran by hypodermoclysis is not indicated as a measure to combat hypotensive states resulting from a diminished plasma volume, since under such circumstances prompt and adequate correction of the existing hypovolemia is essential if the best results are to be obtained.

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INFECTION IN BURNS

III. Septicemia, a Common Cause of Death

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BY MEANS of modern fluid therapy, it is now possible to tide many severely burned patients over the period characterized by enormous and rapid fluid shifts, and death does not frequently occur in the first 2 postburn days. However, the case fatality rate[1] in patients who have full thickness burns involving more than 50 per cent of the body surface has not changed considerably, though survival can frequently be prolonged. Death is usually preceded by high fever, rapid heart and respiratory rates, delirium, gastrointestinal atony, hypotension, and anuria.

The purpose of this report is to record the cause of death in 35 consecutive burn deaths on our service and to focus attention on the problem of septicemia. On the basis of the data that will be presented, it is evident that general invasive infection remains the major unsolved problem in extensively and deeply burned patients.

METHODS

The systemic care of the burned patient and the local care of the burn wounds have been described elsewhere (3, 14, 17).

Blood cultures are taken by a special technique. Face masks are worn by patients and personnel. A vein in an unburned area is used since it is not possible to obtain an uncontaminated blood culture if the needle is inserted through burned skin. The area over the vein is prepared by 3 applications of tincture of iodone, and the iodine is allowed to dry completely between applications. The blood is then drawn by a set composed of a 10 cubic centimeter syringe and a 20 gauge needle, sterilized as a unit in a large test tube. The purpose of this set is to avoid contamination of the needle or the tip of the syringe when the needle is attached. Great care is taken not to contaminate the needle or the plunger. A needle is inserted through the rubber stopper of the media bottle before autoclaving; a gauze sponge fixed in place by a piece of paper that is tied around the neck of the bottle prevents contamination of medium and needle. Before the bottle is inoculated, the needle used for venipuncture is removed, and the tip of the syringe and the hub of the needle in the stopper are flamed. After the inoculation, the needle is extracted from the stopper, which is then painted with tincture of iodine. Five cubic centimeters of blood are injected into one bottle containing 45 cubic centimeters of trypticase soy broth and 5 cubic centimeters into another bottle containing 45 cubic centimeters of thioglycolate broth. The last few drops are placed directly on a blood agar plate.

If the patient has received penicillin, penicillinase is added to each bottle. For patients receiving other antibiotics, the dilution of 5 cubic centimeters of blood by 45 cubic centimeters of culture medium is the only means used to minimize the effects of the antibiotic agent in the cultures. Admittedly, until methods are available for specifically neutralizing each antibiotic agent, such a technique may yield some false-negative cultures.

The inoculated media are incubated aerobically at 37 degrees C. and examined at 24 hour intervals for 4 consecutive days, on the seventh and on the fourteenth days. The cultures are then discarded since it has been shown that blood cultures only rarely show growth after that time. At every examination, two media are inoculated from each bottle: 2 trypticase soy blood agar plates and 2 phenylethyl alcohol blood agar plates. The reasons for using these media are discussed elsewhere (14). At every examination 1 of the trypticase

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[1]The term "fatality rate" is used to designate the number of deaths observed divided by total number of burned patients treated, times 100.

TABLE I.—DEATHS DUE TO CAUSES OTHER THAN SEPTICEMIA

Patient No.	Age, years	Per cent burn		Day of death, days PB*
		Total	3rd°	
Fluid imbalance				
1†	30	55	55	13
2	7	92	87	2
3	21	33	10	7
4	½	59	53	3
5	21	80	40	8
6	34	95	95	1
7	35	71	66	6
8‡	31	86	75	2
9‡	26	64	64	2
Mean ± S.E.§	23±4	71±7	61±9	5±1
Hepatitis				
10	21	19	15	76
11	23	30	26	76
12	18	35	35	78
Mean ± S.E.	21±1	28±5	25±6	77±1
Gastrointestinal ulceration with bleeding				
13†	22	45	25	13
Acute pulmonary damage				
14	33	60	40	1
15	3	30	5	1
16	1½	80	60	0
Mean ± S.E.	13±10	57±15	35±16	0.7±0
Bronchopneumonia				
17	42	60	43	10
Cardiac arrest				
18	27	45	40	87
Cerebral contusion				
19	27	80	80	8

*PB = Postburn. The day of injury is counted as day zero.
†Short case history previously reported by Weigel and co-workers (patient 1 = case 3 and patient 13 = case 1).
‡Patient had acute renal failure.
§S.E. = Standard error = Standard deviation of the mean.

soy blood agar plates and 1 of the phenylethyl alcohol blood agar plates are incubated under anaerobic conditions for 48 hours. The microorganisms are isolated in pure culture on blood agar plates and tested for sensitivity against penicillin, aureomycin, terramycin, chloromycetin, and polymyxin by means of the filter paper disc method. On special indications, sensitivity tests are performed by the tube dilution technique to these as well as to other antibiotics.

If a rapid determination of the sensitivity is important, as it is in cases when septicemia is strongly suspected on a clinical basis, blood agar plates with antibiotic discs are inoculated after only 6 hours of incubation of the media. It is thus occasionally possible to institute specific antibiotic therapy within 24 hours.

This blood culture technique has been repeatedly noted to yield negative cultures in normal, unburned individuals.

RESULTS

Between August 1950 and January 1954, 35 deaths occurred among approximately 700 burned patients treated on our service.

Deaths due to causes other than septicemia. In Table I the deaths other than those caused by septicemia are listed. In the fluid imbalance group, death as a result of fluid imbalance could probably have been prevented in most of the patients if currently accepted standards of fluid therapy had been employed. In patients 1, 3, 5, and 7, serious water deficit was the principal physiologic derangement, as evidenced by clinical signs and symptoms, by a markedly elevated serum sodium concentration, or by heavy water dilution studies. Patient 2 did not receive sufficient quantities of colloid solutions. Patient 4 was given large quantities of 1/6 molar sodium lactate instead of lactated Ringer's solution; death was caused by severe metabolic alkalosis and hypokalemia. Patient 6 had an unusually deep burn of 95 per cent of the body surface. Fluid therapy appeared to be adequate in patient 8; he excreted 420 cubic centimeters of urine during the first 24 hours but none thereafter. Energetic therapy was delayed for 8 hours in patient 9; he did not excrete urine at any time. Hyperkalemia did not occur in either of these patients, and the immediate cause of death is not definitely established; excessive fluid therapy may have been a factor.

The 3 patients whose deaths were caused by an acute, fulminating hepatitis had received pooled, lyophilized plasma as part of the early resuscitative therapy. The clinical features in all of these patients were sudden onset of jaundice, coma, and death within a few days. At the time of death, complete wound closure had been achieved in 2 patients. In patient 12, one more grafting procedure would have been required.

TABLE II.—DEATHS DUE TO SEPTICEMIA

Patient	Age	Per cent burn		Septicemia suspected, days PB	Septicemia proved, days PB	Day of death, days PB	Local care	Organisms cultured and comments
		Total	3rd°					
Septicemia proved								
20	33	47	27	20	27	54	D*	Staph. aur. coag. pos. in 6 blood cultures. Pseudomonas also found in final blood culture 54 days PB. Acute endocarditis
21	26	86	70		15	18	E*	Staph. aur. coag. pos. in 3 blood cultures
22	17	70	45		29	36	D	Proteus in 2 blood cultures. Pseudomonas also found in final blood culture 35 days PB. Acute endocarditis, peritonitis, and meningitis
23	21	72	33		8	11	D	Pseudomonas in 2 blood cultures
24	21	69	35		4	6	D	Pseudomonas in 1 blood culture
25	22	55	50		3	3	E	Paracolon in 1 blood culture
26	27	32	21	5	11	38	E	Staph. aur. coag. pos. hemolytic in 6 blood cultures. Staph. aur. coag. pos. nonhemolytic in 3 blood cultures. Pseudomonas, proteus, paracolon also found in final blood culture 38 days PB. Acute endocarditis
27	8	60	60	14	21	31	E	Staph. aur. coag. pos. in 1 blood culture. Received large doses of ACTH
28†	65	40	25		4	6	D	Aerobacter-klebsiella and paracolon in 2 blood cultures. Received cortisone and adrenocortical extract after onset of septicemia. Acute endocarditis
29	49	40	30		14	22	D	Pseudomonas in 1 blood culture. Received large doses of cortisone for 7 days. Acute endocarditis
30	35	45	45	1	7	8	E	Aerobacter-klebsiella in 3 blood cultures
31	27	60	50	7	11	11	E	Abscesses in myocardium and brain stem. Gram-positive cocci found in the lesions
Mean ± S.E.	29±4	56±5	41±4	—	13±2	20±5		
Septicemia suspected								
32	26	57	56	5		11	E	Temperature 105° F., delirium, and oliguria. Blood culture not obtainable
33†	28	85	70	3		4	E	Pulse 140, cyanosis, and anuria. Received large doses of ACTH. Blood culture not taken
34	26	60	60	19		29	D	
35†	21	45	36	38		65	D	Temperature 104° F. and delirium. Septicemia apparently initiated by eschar excision. Six blood cultures negative. Peritonitis
Mean ± S.E.	25±2	62±8	56±7	16±8	—	27±14		
Mean of combined groups ± S.E.	28±3	58±4	45±4	—	—	22±5		

*D=Local care by occlusive dressing. E=Local care by exposure method.
†Short case history reported previously by Weigel and co-workers (patient 28=case 4; patient 33=case 5; patient 35=case 2).

Patient 13 had large, acute ulcers in the first portion of the duodenum. His clinical course and the pathologic findings have been previously reported (20). Patients 14, 15, and 16 had acute pulmonary damage owing to inhalation of noxious fumes. Patient 17 was intoxicated at the time of burning and aspirated some vomitus. Encircling eschars of the chest, which restricted the respiratory excursions and were not incised until the fifth postburn day, may also have contributed to the development of a severe bronchopneumonia. Cardiac arrest in patient 18 occurred during induction of anesthesia. Patient 19 was in

TABLE III.—SEPTICEMIA WITH SURVIVAL

Patient	Age	Per cent burn		Septicemia proved, days PB	Septicemia cured, days PB	Local care	Organisms cultured and comments
		Total	3rd°				
A	30	23	13	19	26	D	Staph. aur. coag. pos. in 1 blood culture
B	24	45	20	9	15	D	Staph. aur. coag. pos. in 2 blood cultures
C*	27	45	40	4	10	D	Staph. aur. coag. pos. and micrococcus, coag. neg., in 1 blood culture
D	20	25	25	4	14	D	Alkaligenes and gram-positive cocci in 2 blood cultures. Micrococcus coag. neg. in 1 blood culture
Mean ± S.E.	25±2	35±6	25±6	9±4	16±3		

*This patient subsequently died of cardiac arrest during anesthesia (patient 18 of Table I).

a plane crash and incurred a severe cerebral contusion, which was the immediate cause of death.

The mean extent of burn in the fluid imbalance group was 71 per cent of the body surface. All patients except patient 3 had burns extending over more than 50 per cent, and all but patients 3 and 5 had full thickness burns of more than 50 per cent of the body surface. The patients in the hepatitis group had smaller burns, the burns averaging 28 per cent. The mean length of survival in the fluid imbalance group was 5 days. The 3 patients who had hepatitis died on the seventy-sixth, seventy-sixth, and seventy-eighth day respectively. The 3 deaths caused by pulmonary damage occurred on the day of burn or on the first postburn day.

Deaths due to septicemia. The septicemia deaths are listed in Table II. In patients 20 through 30, the presence of septicemia was established by one or more positive blood cultures; in patient 31 multiple visceral abscesses gave evidence of invasive infection. In patients 32, 33, 34, and 35, septicemia was strongly suspected on clinical grounds.

The total extent of burn was more than 50 per cent of the body surface in all but 6 patients, and the extent of full thickness burn was 50 per cent or more in 7 patients. The mean total extent was 58 per cent, and the mean full thickness skin loss was 45 per cent.

In some of the patients, septicemia was suspected on clinical grounds several days before the diagnosis was established by blood culture. On the average, septicemia was proved on the thirteenth postburn day. The mean survival time of 22 days in the septicemia patients is longer than the mean survival time of 5 days in the fluid imbalance patients ($P<0.02$).

Of the 16 patients who had proved or suspected septicemia, 8 were treated by the exposure method and 8 by occlusive dressings in the early postburn period. The severity of injury and time of survival are comparable in these subgroups.

Penicillin in large doses was used routinely for the first 3 or 4 days. Thereafter, most patients received one of the broad spectrum antibiotics. When microbes were isolated from the blood stream, specific chemotherapy as determined by sensitivity tests was instituted in all cases. In all patients but 1 (No. 35), the eschars were undebrided, only partially debrided, or had been recently excised.

Staphylococcus aureus, coagulase positive, was the causative organism in 2 patients. In 2 others, this microbe was the predominant organism, but gram-negative bacilli were also isolated shortly before death. In the remaining 7 patients, various gram-negative bacilli were isolated from the blood stream (pseudomonas, proteus, paracolon, aerobacter-klebsiella).

Septicemia with survival. Four patients who had septicemia recovered (Table III). Although this is a small group, the mean extent of burn (35 per cent) differs ($P<0.01$) from the mean extent in patients who succumbed to septicemia (58 per cent). Similarly, the mean extent of full thickness burn differed in these respective groups ($P<0.05$). Treatment, similar to that given in the fatal cases, consisted of careful wound hygiene and specific systemic antibiotic therapy in large doses.

DISCUSSION

Over-all fatality. The case fatality rate in burns appears to vary in different reports. In a series of 744 consecutive burns, Bettman (1946) recorded 23 deaths, 5 of which were caused by infection. In 800 burns, Clarkson and Lawrie (1946) reported infection as the cause of death in 4 of the 16 deaths that occurred. In Sen's series (1948) of 160 burned patients, there were 29 deaths, 3 of which were caused by infection. Colebrook reported a case fatality rate of 1.7 per cent in 241 burned children treated at the Birmingham Burns Unit in 1946 to 1947 and pointed out the marked decline in the case fatality rates since the late 1920's when Fraser recorded a case fatality rate of 30 per cent in 300 burned children. In 734 patients treated in 1945 to 1947, Colebrook reported an over-all case fatality rate of 4.7 per cent. He believed that this decrease was a reflection of improved shock therapy and better control of infection.

In assessing the fatality rate, these statistics must be interpreted with great caution. Fatality in burns is known to be influenced in large measure by the extent and depth of burn. In a large series of minor burns, the case fatality would be expected to approach zero. Probit analysis, as described by Finney, makes possible a more acceptable comparison of fatality statistics. This technique has been recently introduced in the study of burns by Bull and Squire at the Birmingham Burns Unit and by Moyer in St. Louis. When analyzed by the use of probits, fatality in burns does not vary significantly between units that differ greatly in the methods of local care employed. A comparable analysis based on the data from our unit (18) indicates that our fatality is closely comparable to that recorded by others. The factors responsible for death are likely to be the same in all burn centers.

Nonsepticemia deaths. The number of deaths caused by fluid imbalance could probably be greatly reduced by the energetic fluid regimens that have been developed during the past few years. Since most of the patients in the fluid imbalance group were extensively burned and since their mean length of survival was significantly shorter than that of the patients in the septicemia group, it is quite possible that ever-improving fluid therapy may allow more patients to survive long enough to develop septicemia.

Discontinuation of the use of plasma that is likely to be contaminated by the virus of homologous serum hepatitis will markedly reduce the number of hepatitis deaths in the future.

When serious pulmonary damage exists owing to the inhalation of fumes, the fatality is known to be high, even when the burn is only trivial. This problem is formidable and, at present, treatment is not entirely satisfactory. In our patients, the incidence of pulmonary damage was fortunately low, but it must be recognized that pulmonary damage can be a major cause of death.

SEPTICEMIA

In this series of patients, it is clear that the cause of death could be established in most instances. The two major groups, fluid imbalance and septicemia, account for the great majority of deaths.

If the presence of septicemia had not been recognized, 16 of the 35 deaths would have been classified as resulting from unknown causes. Perhaps these deaths would have been ascribed to toxemia or to some other equally obscure and ill-defined pathologic entity. Many of the unexplained deaths recorded in the literature are probably deaths caused by invasive infection, for the clinical picture described is frequently indistinguishable from septicemia.

The signs and symptoms of overwhelming septicemia in burns are very characteristic. The temperature is usually high (104 to 107 degrees F.). Only rarely is it possible to reduce the fever to below 102 degrees F. by antipyretics and by frequent cold sponging. Marked fluctuations in temperature do not generally occur. Sinus tachycardia (140 to 170 per minute) is nearly always noted, and a rapid respiratory rate (30 to 60 per minute) is characteristic. The patient is disoriented. There is a severe hypotension that is refractory to infusions of blood and electrolytes, and the urinary output is scanty or absent. Paralytic ileus is commonly observed. Not infrequently, the signs and symptoms of sep-

ticemia appear suddenly. The patient's general appearance may be entirely satisfactory for a time and then, suddenly, a full blown picture of septicemia may be evident. In some of the patients, jaundice is evident clinically, and petechial hemorrhages may be present in the unburned areas. The jaundice is probably of the hemolytic variety, but detailed studies to substantiate this have not been performed in our patients.

Clearly, such a clinical syndrome would be well characterized as toxemia. In some instances, a mistaken diagnosis of adrenocortical insufficiency could be easily made. In 1 of the patients (No. 28), this serious mistake was actually made, and adrenocortical replacement therapy, which was instituted on the basis of an erroneous diagnosis, probably contributed to the rapidly fatal outcome. There are some suggestions in the literature that similar mistakes are not infrequent and that they may remain undetected. The term toxemia has been used to describe a great variety of pathologic entities in burns. Although it is difficult to draw a clear distinction between these, the term toxemia appears to have been used in connection with water intoxication, hepatic necrosis resulting from tannic acid therapy, as well as invasive infection. A great abundance of investigative efforts has failed so far to demonstrate convincingly the existence of a burn toxin derived from the denatured protein of the burn tissue. Calling a disease by its proper name is a step in the right direction. It is too easy to hide behind the term toxemia, which implies absolution from having allowed invasive infection to occur and obscures the fundamental issues. The probability is great that bacteria and their products and not noxious substances of burned tissue are largely responsible for death in burned patients. This concept is far from new. Aldrich presented evidence of the bacterial origin of the toxemia syndrome in burns in 1933. In recent years, Cope (8) has emphasized the relationship between toxic and infectious complications of burns.

Awareness of the problem of septicemia is essential to the diagnosis of this frequently fatal complication. In the patients studied, the onset of septicemia probably preceded the time of a positive diagnosis by many days. Blood cultures were not always obtained sufficiently early nor sufficiently frequently. A blood culture technique that yields few false-positive and few false-negative results is essential to successful diagnosis. The technique described appears to be satisfactory in both respects. It is likely that the incidence of nonfatal septicemia in this series is low only because blood cultures were not obtained, or obtained too infrequently, during the early part of the study. Many patients who are less severely burned probably develop septicemia and recover, but the diagnosis escapes recognition.

The type of early local care does not appear to be a crucial factor in determining whether or not septicemia occurs, since half of the patients who developed fatal septicemia were treated by occlusive dressings and half by the exposure method. The core of the septicemia problem may well lie in the enormous bacterial inoculum that resides in or beneath the extensive eschars. Meleney has shown that the depth of the burn and the amount of tissue damage are the main factors determining the severity of infection. In partial thickness burns that are properly treated, infection is rarely a formidable problem; as the depth and extent of burn increase, infection becomes increasingly dangerous. Finland, Cope and associates (9) and Altemeier have emphasized that general invasive infection is particularly apt to occur in full thickness burns during the early postburn period.

The large pabulum for bacterial reproduction that extensive eschars supply may allow the microbes to enter the blood stream in such large numbers that the host defenses are overcome and chemotherapy does not suffice. To make matters worse, severely burned patients are difficult to maintain in good nutritional balance, debilitation of some extent is the rule, and the patient's capacity to resist infection is probably impaired. Serious injury alone may impair the immune responses, either through the release of endogenous adrenocortical hormones or through some other mechanism, but information about this vital problem is very scanty. The output of adrenocortical hormones is very high after

burns, and in experimental animals inhibition of antibody formation occurs under certain conditions when cortisone is given. In 4 of the patients presented, ill-advised therapy with ACTH or cortisone appears to have been an aggravating factor (patients 27, 28, 29, and 33).

In hemorrhagic shock in dogs, Fine and his co-workers have presented evidence that bacteria from the gastrointestinal tract may invade the blood stream. In our patients, hypotension never preceded the onset of septicemia but always followed it. Although the recovery of additional microbial species shortly before death in patients 20, 22, and 26 suggests that invasion from the gastrointestinal tract may have occurred in the terminal stages, it is much more likely that the primary source of bacterial invasion in burns is the large necrotic wounds. In all of the proved septicemia cases, the microbes recovered from the blood stream were also present in great abundance on the wounds. In 3 patients (No. 26, Table II; B and C, Table III), Staphylococcus aureus, coagulase positive, of the same bacteriophage type was recovered from the wounds and the blood stream. The bacteriophages failed to lyse either the wound or the blood stream staphylococci in 2 other patients (No. 20, Table II; A, Table III). Bacteriophage typing was not performed in the remaining 2 patients who had a staphylococcal septicemia (Nos. 21 and 27).

Treatment of septicemia. The treatment of septicemia in extensively and deeply burned patients is totally unsatisfactory at present. Although antibiotics have largely eliminated invasive infection by group A beta hemolytic streptococci as a cause of death and appear to be beneficial in the treatment of less severely burned patients, they have not by any means solved the problem of infection in burns. All of the antibiotics now available have been used in varying dosages, singly and in combinations, but without success in the 16 fatal cases. In all instances, the microbes recovered from the blood stream were sensitive in vitro to one or several antibiotics. Despite this, sterilization of the blood stream could not be achieved, and the patients died from relentless septicemia.

Future approach to the problem of septicemia. Since presently known methods of treatment, for septicemia, once it has developed, are so ineffective, it would seem that, in the future, therapy should be directed at prevention of this frequently fatal complication. The relationship between the size of the wound and the incidence of fatal septicemia focuses attention on the need for wound closure at the earliest possible time. Excision of the eschars in stages, starting not later than the fourth postburn day, and application of autografts, homografts, or both, appear to be logical. The feeding inoculum may thus be reduced, and septicemia may be prevented. Since exposed subcutaneous tissue offers a ready avenue for invasive infection, it may be best to apply the grafts immediately after the excision of the eschars rather than wait for the development of granulations. If such a regimen of excision and grafting is employed, a rigorous time table should be maintained until at least temporary coverage of large parts of the wounds is achieved. This approach may seem somewhat heroic and is not without danger, but there are indications that it holds some promise.

Excision during the second postburn week is a common practice in the management of patients who are not burned too extensively. In very severe burns, this may be too late, but most surgeons hesitate to excise eschars before the patient's general condition has become stabilized. Between the fifth and twelfth day, the patient is generally quite ill, and the surgeon's reluctance to subject the patient to the further stress of anesthesia and surgical excision is understandable. The usual procedure in very extensively burned patients is to await the natural sequestration of eschars. If this occurs and a granulating barrier is established, the danger of septicemia is considerably lessened. However, during the waiting period, very extensively burned patients frequently develop a fatal septicemia.

The decision to excise eschars boldly in stages during the immediate postburn period is difficult to make. On the other hand, the fatality rate in patients who have full thickness burns of more than 50 per cent of the body surface is almost 100 per cent. Many such patients, if treated by a proper fluid

regimen, will survive the initial postburn period and develop septicemia later. It would seem that a logical approach to the management of patients with massive burns would be prevention of septicemia by removal of the eschars in the immediate postburn period and the application of homografts.

SUMMARY

In an analysis of 35 consecutive burn deaths, the cause of death could be definitely ascertained in 29 of the patients. Death was caused by fluid imbalance in 7 patients, septicemia in 12 patients, respiratory tract damage in 3, fulminating homologous serum hepatitis in 3, gastrointestinal hemorrhage in 1, cardiac arrest in 1, bronchopneumonia in 1, and cerebral damage in 1.

Two patients had acute renal failure and may have died as a result of excessive fluid therapy. In 4 patients, septicemia was strongly suspected but not proved.

The data presented indicate that septicemia rather than toxemia is a principal cause of death in burns. When this is recognized, most burn deaths can be explained.

In the severely burned patients, antibiotics have failed in the prevention and treatment of septicemia.

A vigorous regimen of early excision of eschars and skin coverage is proposed as a logical approach to the therapy of extensively and deeply burned patients.

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OBSERVATIONS ON THE INTERSTITIAL PORTION OF THE FALLOPIAN TUBE

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THE medical literature contains relatively few references to the anatomy and histology of the interstitial portion of the fallopian tube. No references were found in the several textbooks on anatomy and but few in the many monographs on gynecologic pathology which were consulted. Most of the work has been carried out as studies of the sterility problem. Many of the early reports were from German investigators. Philipp and Huber (2, 5) in 1939 published a comprehensive study. In the American literature, the communication during 1925 of Geist and Goldberger is among the earliest. Rubin (6, 7) carried out intensive investigations over a period of years in connection with his studies on uterotubal insufflation and published his observations in the monograph on insufflation. During the study of this portion of the tube begun in an attempt to obtain data in regard to the size of the lumen, many features of its histoanatomy were observed, which, as far as could be determined, had not previously been noted. These observations form the basis of this report.

MATERIAL AND METHODS

The material consisted of 300 uteri obtained from 259 hysterectomies and 41 autopsies. After the uterine cavity was exposed through a longitudinal incision, the specimens were fixed in neutral 10 per cent formalin solution. The uteri were usually sectioned according to the diagram illustrated in Figure 1, each block being approximately 3 millimeters in thickness. In a few instances, the tubes were cut longitudinally. The total number of tubes successfully sectioned was 554. One or more sections were obtained routinely from each block. In a few cases, specific blocks were sectioned serially. The routine stain employed was hematoxylin and eosin. In several cases, it was supplemented with the trichrome, Van Gieson, and reticulum or Mallory phosphotungstic acid stains, and occasionally with an elastic tissue stain.

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OBSERVATIONS

Race and age. Among the 300 cases, there were 264 white women and 36 negresses. The age distribution ranged from 4 months gestation to 87 years.

Associated pathologic anatomy of the corpus uteri. In 65 cases, the uterine body was normal or free of changes which could cause pathologic distortion of the interstitial segment of the fallopian tube. This group covered the full age range represented in the entire series from fetal development to 87 years. Included were 1 anomaly, a double uterus (3), 2 intrauterine pregnancies, 2 postpartum uteri, and 5 endometrial carcinomas.

In 65 cases uterine fibroids were present. The age range was from 29 to 76 years. Two cases were associated with intrauterine pregnancies, 2 with leiomyosarcoma, and 1 with carcinosarcoma of the endometrium (4).

In 59 cases the uterus was involved with adenomyosis. The ages in this group ranged from 23 to 74 years. Five were complicated by endometrial carcinoma.

In 111 cases both fibroids and adenomyosis of the uterus were noted. The youngest in this group of patients was 28, the oldest 64 years of age. Intrauterine pregnancy was the complication in 3 cases and endometrial carcinoma in 10. The data are summarized in Table I.

Histoanatomy of the interstitial segment. The interstitial segment of the fallopian tube, measured from its junction with the cornual end of the extramural portion to its internal

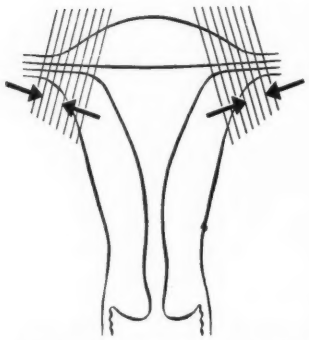


Fig. 1. Schema for sectioning of uterus. The interstitial segments of the tubes lie between the arrows.

ostium at the funnel of the uterine cavity, is 1 centimeter or less in length. The length is estimated from the number of blocks of tissue which show this segment histologically. As noted previously, the blocks were cut 3 millimeters thick. It was rare to find the fallopian tube occupying more than 3 blocks. The interstitial segment, therefore, was judged to be 1 centimeter or less in length. It does not equal the entire thickness of the uterine wall (Fig. 2). The shape is that of a cone. The tip of the cone fuses with the cornual part of the extramural tube and the proximal part with the myometrium. At the external uterotubal junction, there is a short segment surrounded by the uterine vessels as they enter and leave

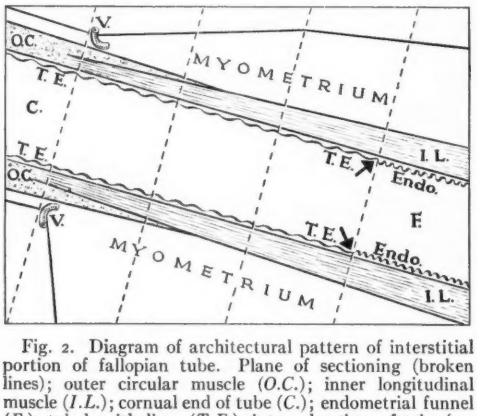


Fig. 2. Diagram of architectural pattern of interstitial portion of fallopian tube. Plane of sectioning (broken lines); outer circular muscle (*O.C.*); inner longitudinal muscle (*I.L.*); cornual end of tube (*C.*); endometrial funnel (*F.*); tubal epithelium (*T.E.*); internal ostium of tube (arrows); endometrium (*Endo.*); vessels at uterotubal junction (*V.*).

the uterus. In this area (Fig. 3), the vessels separate the segment from the myometrium. As the vessels branch and ramify in the uterine wall, the muscular wall of the tube fuses with the uterine musculature. The interstitial segment of the tube has two components, a muscular coat and a mucosa. The muscle has two layers, an outer circular and an inner longitudinal layer (Figs. 3, 4 and 5). The outer circular coat is a continuation of the muscle of the extramural part of the tube. It loses its circular pattern a short distance after the fusion of the tubal muscle and the myometrium (Fig. 4). The inner longitudinal coat is a continuation of the subendometrial muscle at the funnel of the uterine cavity (Fig. 6). It retains its pattern until it fuses with the musculature of the cornual end of the extramural tube. The longitudinal muscle is rich in large channels lined by endothelium (Figs. 3 to 7). They apparently are blood vascular in nature. Attempts to inject these vessels through the artery and vein were unsuccessful. However, in 3 cases of extensive venous thrombosis, they contained blood. An anatomic uterotubal sphincter could not be demonstrated.

The mucosa is characterized by a single layered columnar epithelium, and a villous pattern. Usually the basement membrane rests upon the muscle (Figs. 3 to 9), occasionally upon the vascular channels (Fig. 7). Sometimes a thin layer of reticulum separates them. The villi have a moderate amount of reticulum fibers which are slightly more abundant near the internal ostium of the tube at the junction with the uterine cavity and are more prominent in the postmenopausal period. At the internal ostium, there is usually an abrupt change between the endometrium and the tubal epithelium (Figs. 6a and 8). Occasionally there is a gradual transition, making it difficult to draw a sharp line of transition between the tube and the funnel. In the fetus and during infancy, childhood, and adolescence, the epithelium is indistinguishable from that of the endometrium. During the period of reproduction, it usually has the character of the epithelium found in the extrauterine portion of the tube. However, it is fairly common to encounter con-

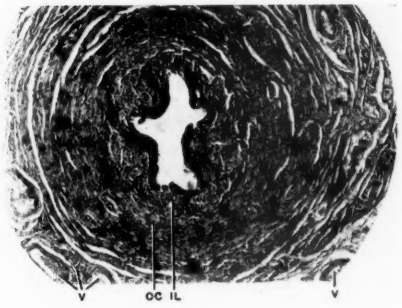


Fig. 3.

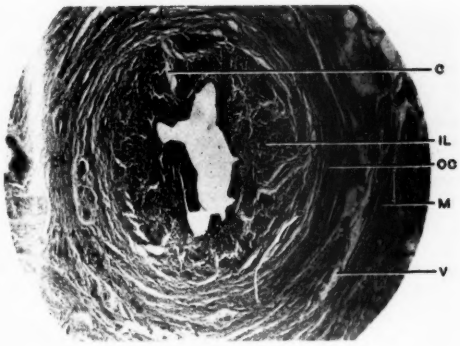


Fig. 4.

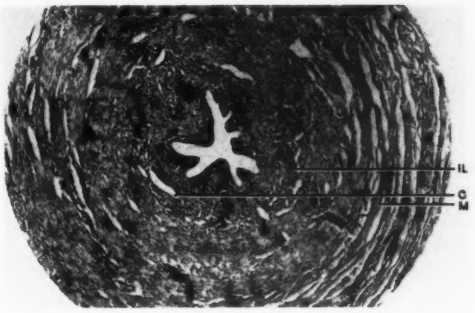


Fig. 5.

Fig. 3. Cross section through distal third of interstitial segment of fallopian tube. The mucosal pattern is simple and the epithelium of single layered columnar type. The inner longitudinal muscle (*IL*) is thin. The outer circular muscle (*OC*) is heavy. External to the circular coat are the blood vessels (*V*) at the uterotubal junction separating tube from myometrium which is not visible in photograph. Compare with Figure 2. ×17.

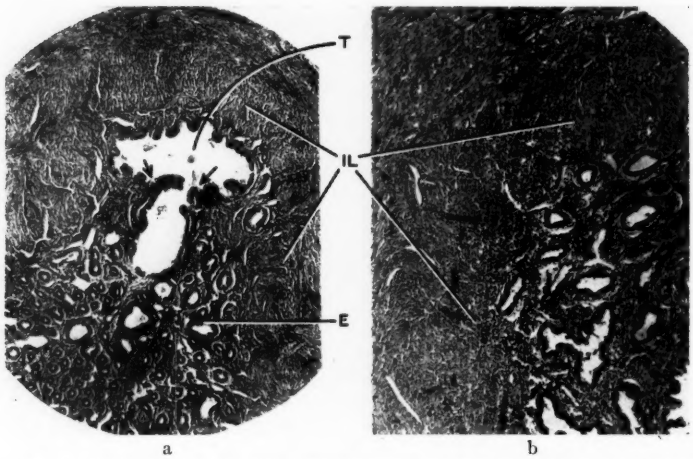
Fig. 4. Cross section through midportion of interstitial segment of fallopian tube. The mucosal pattern is mainly simple with one long villus. The single layered cylindrical epithelium rests directly upon the inner longitudinal muscle layer (*IL*) which is thick and richly vascular (*C*). The outer circular muscle (*OC*) is beginning to show fusion with the myometrium (*M*), the vessels (*V*) being smaller in size than through the distal portion shown in Figure 3. Compare with Figures 2 and 3. ×19.

Fig. 5. Cross section of proximal portion of interstitial segment of fallopian tube. The mucosal pattern is simple, the epithelium tall, columnar, and resting directly upon the stout inner longitudinal muscle (*IL*). The muscle has many large vascular channels (*C*) and shows fusion with the myometrium (*M*). Compare with Figures 2, 3, 4. ×18.

siderable difficulty in differentiating it from the uterine epithelium and occasionally it appears typically uterine in nature. Very slight changes may occur in the postmenopausal period, although there is a marked tendency in the older ages for epithelial atrophy progressing to complete loss and atresia (Fig. 11). The villous pattern is present at all ages, including the fetal, and is extremely variable in appearance. The pattern varies, not only between right and left sides but within the interstitial segment itself. It may be very simple, producing a cross bun appearance, or may be so complex as to resemble the ampulla (Figs. 3 to 10, 12, and 13). A few cases show nests of normal lymphoid tissue, such as are found in the normal endometrium. In summary, the mucosa of the interstitial portion of the fallopian tube has characteristics common to both the extramural portion of the tube and to the endometrium.

Findings in the interstitial segment of the fallopian tube. The following conditions were discovered in the specimens examined:

1. Tubal endometrium. Endometrium was present in the mucosa of the interstitial segment in 75 cases, 25 per cent of the entire series. In 64 per cent, 48 cases, it was unilateral; in 24 per cent, 18 cases, it was bilateral. In 9 instances, only one side was satisfactory for study. It varied in extent from a complete endometrial lining to isolated foci (Fig. 10). The ages of these patients ranged from 23 to 75 years. According to the distribution by decades, there were 2 in the third, 20 in the fourth, 38 in the fifth, 11 in the sixth, and 2 each in the seventh and eighth decades. There were 70 white women and 5 negresses.



a b

Fig. 6. Continuity of longitudinal subendometrial muscle of uterine funnel and inner longitudinal muscle of adjacent portion of interstitial segment of fallopian tube. a, A slightly oblique section (×21) showing endometrium (*E*), internal ostium of tube (arrows), proximal portion of tube (*T*), inner longitudinal muscle of tube and subendometrial muscle of funnel (*IL*). b, A cross section of uterine funnel (×31) slightly more mesial than the level shown in a. Compare with Figures 3, 4, and 5.

2. Atresia. Cicatricial atresia from inflammatory disease was found in 4 instances (Fig. 11a). Three were associated with salpingitis, 1 with chronic endometritis accompanying fibroids. In another instance, the atresia was due to a small adjacent fibroid, possibly modified by previous inflammation. The youngest age at which the senile type of atresia (Fig. 11b) was found was 49 years.

3. Stenosis. Stenosis was uncommon. It was usually caused by polyps originating from the mucosa. In 2 instances, polyps of the endometrium arising near the internal ostium of the tube caused stenosis by projection up into the lumen (Fig. 12). Fibroids almost never produced narrowing.

4. Polyps. Polyps were present in the tube in 33 cases, 11 per cent of the entire series. They were always endometrial in nature and arose from isolated endometrial foci (Fig. 13a). They were not found in tubes in which the mucosa consisted only of endometrium and lacked tubal epithelium. They comprised 44 per cent of the 75 cases in which endometrial tissue was found in the tubal lumen. In 2 instances, the polyps were partly endometrial and partly tubal in nature (Fig. 13b). Usually the endometrium of the polyp was nonfunctioning. One showed a secretory phase, 4 were decidual. When present in the postmenopausal period, they displayed the changes compatible with the age. One polyp was fibrosed, another appeared senile cystic.

TABLE I.—AGE AND NORMAL AND PATHOLOGIC UTERINE ANATOMY OF 300 PATIENTS

Age	Normal	Fibroid	Adenomyosis	Fibroid and adenomyosis	Total
Fetus	6	0	0	0	6
NB–10	9	0	0	0	9
11–20	2	0	0	0	2
21–30	8[a c]	2	2	2	14
31–40	15[a e]	21	16	27[b e]	79
41–50	6	28[b i]	23[e]	60[a f]	117
51–60	3[e]	8	12[d]	18[g]	41
61–70	5[f]	5[h i]	5[e]	4[d]	19
71–80	7	1	1	0	9
81–90	4	0	0	0	4
Total	65	65	59	111	300

a—1 intrauterine pregnancy
b—2 intrauterine pregnancies
c—1 postpartum uterus
d—1 endometrial carcinoma
e—2 endometrial carcinomas
f—3 endometrial carcinomas
g—4 endometrial carcinomas
h—1 endometrial carcinosarcoma
i—1 leiomyosarcoma

5. Papilloma. A solitary instance of papilloma was found (Fig. 14). It was present in the distal part of the interstitial portion of the right tube in a negress 45 years of age, the uterus and both adnexa having been removed for fibroids.

6. Primary carcinoma. A lesion which had the histologic criteria of noninvasive carcinoma was found in the interstitial portion of the tube in 1 instance (Fig. 15). The patient, a white woman 50 years of age, had a complete hysterectomy and bilateral salpingo-oophorectomy for severe adenomyosis. The ovaries and the extramural portions of the tubes were normal and the interstitial segments free of endometrial nests. In the distal portion of the right interstitial tube, all the sections from one block showed a mucosa lined by a single layer of bizarre cells displaying anisocytosis, macronucleation, cytoplasmic and nuclear hyperchromatism, normal and bizarre mitoses, and some desquamation. At the edge of the lesion, near its fusion with the cornual end of the tube, there was a sharp transition from the normal to the abnormal epithelium. The underlying tissue was engorged, edematous, and infiltrated with lymphoid and eosinophilic cells. Adjacent blocks on each side showed normal tissue.

There was no instance in which tubal endometrium showed malignant transformation.

7. Endometrial carcinoma. Among the 20 cases of endometrial carcinoma, 4 showed tubal involvement. One case presented a plypoid tumor extending from the main tumor into the tubal lumen. It duplicated the pattern of the polyp previously noted and illustrated in Figure 12. In 2 cases there was surface extension into the tube (Fig. 16b). In 1 case, in which the myometrial veins were invaded, the small vessels of the inner muscular coat were also affected (Fig. 16a).

8. Secondary ovarian carcinoma. There was 1 case of ovarian carcinoma invading one side of the uterus. The carcinoma extended down into the lumen of the interstitial part of the tube as a polypoid mass.

DISCUSSION

The length of the interstitial portion of the fallopian tube has been reported as varying from 1.5 to 5 centimeters. Our own observations would suggest that this portion of the tube is somewhat shorter. Our conclusion is based on the findings in normal tubes which lack any endometrial mucosal lining. The architectural pattern of the musculature, being similar in nature in the proximal interstitial portion of the tube and in the endometrial funnel, fails to give a criterion for distinguishing one from the other. The size of the lumen also fails to give a sound criterion, because the lumen of the endometrial funnel has practically the same dimensions as that of the adjacent portion of the tube. In the

Fig. 7. The large blood vascular channels present in the inner longitudinal muscle of the interstitial segment of the fallopian tube. The epithelium lies directly upon the wall of the vessel. ×189. Compare with Figures 3, 4, 5, and 6.

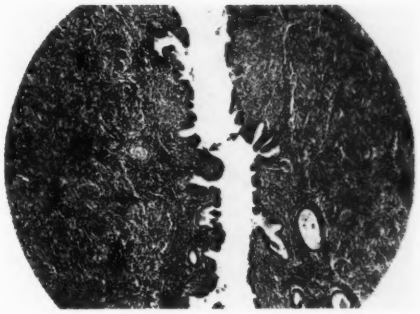
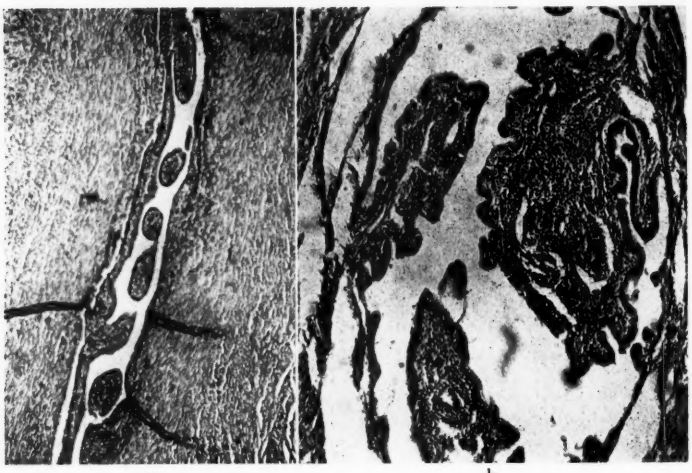


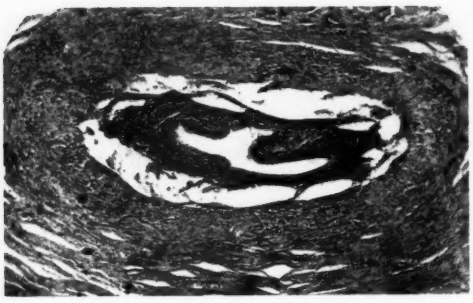
Fig. 8. Longitudinal section of proximal portion of the interstitial segment of the fallopian tube and the distal portion of the endometrial funnel. At the internal ostium of the tube (arrows) there is a sharp transition between the single layered cylindrical epithelium of the tube (upper) and the endometrium with its glands and stroma (lower). The tubal lumen and the endometrial funnel are the same size. ×13.



a b

Fig. 9.

Fig. 9. Mucosal patterns of the interstitial segment of the fallopian tube. Both areas are from the proximal part of the tube in two different cases. a, Longitudinal section showing a very simple polypoid pattern. The inner longitudinal muscle is distinct. ×35. b, Cross section showing a very complex polypoid pattern somewhat like the ampulla of the extramural part of the tube. Compare with Figures 3, 4, 5, 8, and 13.



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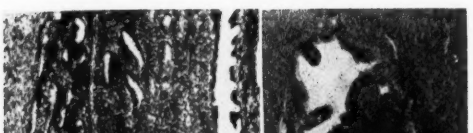


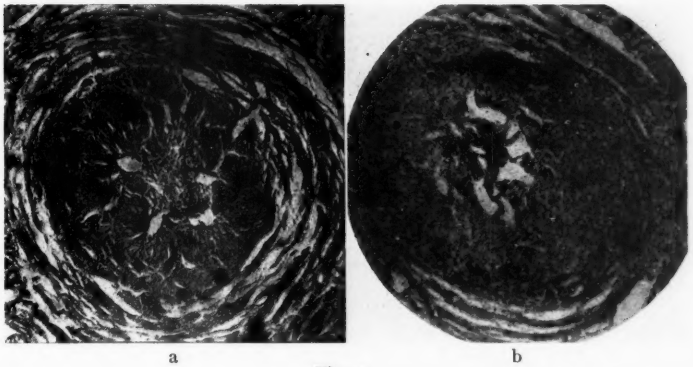
b c

Fig. 10.

Fig. 10. Interstitial tubal endometrium. a, Distal portion of a tube whose mucosa consists of endometrium only. ×25. b, Proximal portion of a tube whose mucosa is tubal on one side and endometrial on the opposite side. ×25. c, Proximal portion of a tube with an isolated focus of endometrium lying in the tubal mucosa. ×18.

majority of cases, there is a sharp differentiation between the endometrium and the tubal mucosa. A transition zone was only occasionally encountered. This point of differentiation marks the internal ostium of the tube. Measured from the internal ostium, the interstitial portion of the tube is considerably shorter than the measurements given in the literature. The uterine horn which shows a very small lumen appears to have two components, the interstitial portion of the tube and the endometrial funnel. We believe that many of the measurements reported in the literature have included both components.

There was not encountered in the present series, the dilation of the mesial segment of the tube noted by Schneider and called by him the antrum tubae. The method of investigation employed by Schneider probably accounts for the difference in our anatomic findings. In his work, the freshly extirpated uterus was injected with a contrast medium



a b

Fig. 11.

. 11. Atresia of interstitial segment of fallopian tube. a, tinflammatory atresia. The lumen is obliterated by fil s tissue. The muscle is unaffected. ×22. b, Senile at a. The lumen is unidentifiable and scar tissue ab t. ×11. In both sections, the vascular channels of th ternal longitudinal muscular layer are very promi- n Compare with Figures 3, 4, 5, 6, and 7.

g. 12. Stenosis of the interstitial segment of the fa ian tube. An endometrial polyp arising from the e metrium of the funnel near the internal ostium of the t projects upward into the tubal lumen. ×17.

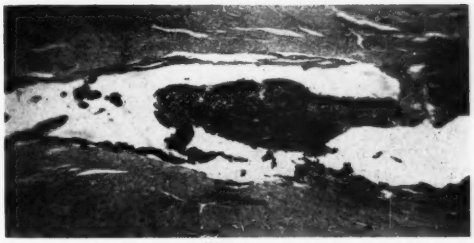
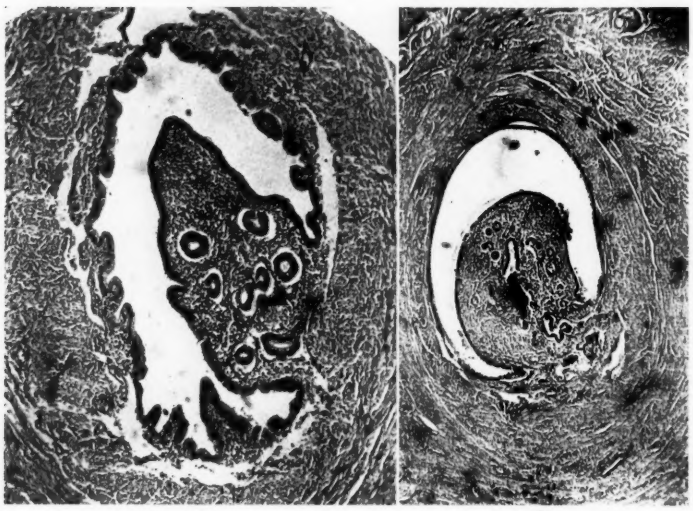


Fig. 12.

and exposed to the x-ray film. Under fluoroscopic control, the specimen was marked with pins at the area indicating the tuboendometrial junction. The specimens were fixed and cut longitudinally instead of at right angles to the lumen, as in our work. In the few specimens cut longitudinally, the antrum was not demonstrable. Apparently, the antrum is seen in the living state and is produced by injection of a contrast medium into the uterus and tubes and is not demonstrable in specimens not thus injected, although they are fixed in formalin solution very shortly after extirpation.

The presence of a stout inner longitudinal muscular coat and the absence of an anatomic uterotubal sphincter, in agreement with other observers, appears confirmed. It is theoretically possible that the contraction of the longitudinal muscular layer, which is uniquely located innermost along the centimeter length of the interstitial segment of the tube, may have a sphincteric action. Because of its relatively sparse muscular components, the outer circular coat probably plays a minor or auxiliary part in the sphincteric action which has been demonstrated on x-ray films.

The question arises as to the significance of endometrium in the interstitial portion of the fallopian tube. In medical literature, its presence has been called "tubal endometriosis." The term implies a pathologic condition. It has also been held that it is a normal developmental phenomenon, and not necessarily a pathologic condition, although it may be the basis for pathologic change. When one considers that endometrium within the lumen of the interstitial segment of the tube is found in 1 out of every 4 specimens, that it is seen at all ages past the second decade of life in uteri free of fibroids or adenomyosis or pelvic inflammatory disease, and that the interstitial portion of the tube normally may have features of endometrial character, the assumption of endometrial dislocation as such is not necessarily supported by the present findings. There is as much justification for the belief that the differentiation of epithelium may



a b

Fig. 13.

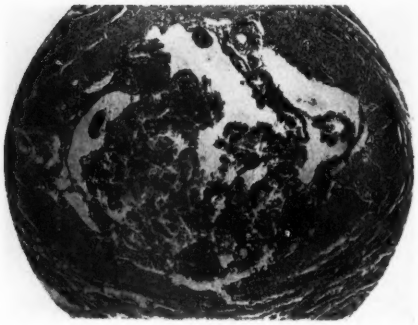


Fig. 14.

Fig. 13. Polyps of the interstitial portion of the fallopian tube from two different cases. a, Endometrial polyp showing glands and stroma. The tubal epithelium has a small villous pattern. The vessels of the inner longitudinal muscle are prominent. ×34. b, Polyp partly endometrial with glands and stroma and partly tubal with single layered epithelium and fibrous core. The remainder of the lumen is lined by tubal epithelium showing pressure atrophy, evidence of a stenotic process. ×20.

Fig. 14. Papilloma of the interstitial segment of the fallopian tube. The site of origin is the tubal epithelium of the distal third of the interstitial segment. ×22.

swing in either direction at or after puberty in response to the new hormonal upswing taking place in the person at that period of life.

Another question which arises concerning the presence of endometrium within the interstitial tube is its possible relation to salpingitis isthmica nodosa. Philipp and Huber have demonstrated in some of their cases the development of typical adenomyosis originating from interstitial tubal endometrium. Similar lesions were not found in the present series. The closest approach was one tube which showed glands beyond the tubal lumen lined by epithelium of tubal nature, and not accompanied by endometrial stroma. A connection between the glands and the tubal lumen could not be demonstrated. The tubal mucosa was free of endometrium. There were 8 other cases with tubal endometrium in which adenomyosis was limited to the adjacent uterine wall, sometimes producing the gross deformity found in salpingitis isthmica nodosa. In each instance, the origin of the adenomyosis was from the endometrium of the funnel; it surrounded the interstitial tube but did not communicate with its lumen. The observations of Geist and Goldberger are similar to ours. In none of their cases of cornual adenomyosis could they demonstrate continuity between the tubal lumen and the adenomyotic glands.

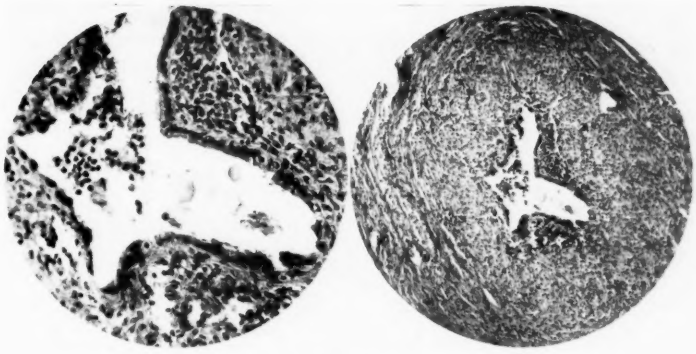


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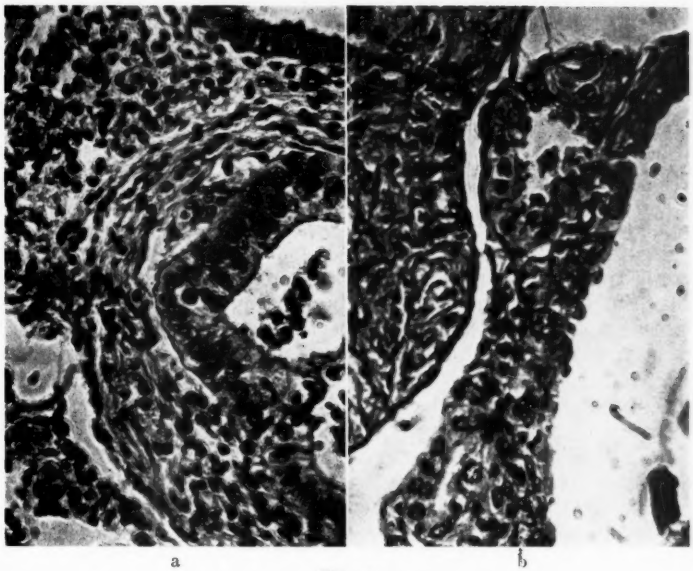
Fig. 15.



a b

Fig. 16.

Fig. 15. Primary carcinoma of interstitial segment of fallopian tube. Origin is from tubal epithelium in distal third of interstitial segment. Section shows edge of neoplasm and junction with normal epithelium. a, ×135. b, ×47.

Fig. 16. Extension of endometrial carcinoma into interstitial segment of fallopian tube. a, Venous permeation of vessels of inner longitudinal muscle. b, Surface extension. ×238.

A further question which arises is the possible causal relationship between tubal endometrium and endometriosis of ovaries and peritoneum. Philipp and Huber strongly emphasize this interpretation. Among 283 patients 21 years of age or over in the present series, there were 13 cases, 4.6 per cent, of endometriosis affecting ovaries or peritoneum. In 11 instances, the diagnosis was made by microscopic examination of one or both adnexa. In 2 instances, the diagnosis was made at operation. Both adnexa were available for study in 133 of the 283 cases. Tubal endometrium was present in 28 cases, 3 of

which were associated with endometriosis. Tubal endometrium was absent in 105 cases and endometriosis was present in 7. In 53 cases only one adnexa was available for study. In 15 of the 53 specimens tubal endometrium was noted while endometriosis was seen in only 1. Thirty-eight were free of tubal endometrium and endometriosis was absent. Among the 75 specimens with tubal endometrium, endometriosis was present in 4 instances, 5.3 per cent. In the 208 cases without tubal endometrium, there were 9 instances of endometriosis, 4.3 per cent. The differences in the percentages of endometriosis in the entire series and in the cases with and without tubal endometrium are insignificant. They do not support the contention that the presence of endometrium in the interstitial portion of the fallopian tube has a causal relationship to the development of extrauterine endometriosis.

The last question is the possible effect of tubal endometrium on the incidence of pregnancy. In the 75 patients showing tubal endometrium, data were available for analysis in 57. Normal intrauterine pregnancies had occurred in 42 patients. The number of pregnancies ranged from 1 to 7, and 2 patients had borne twins. Fifteen of the 42 patients had histories of abortion, usually spontaneous. Three of them had never successfully gone through a normal pregnancy. Fifteen patients had never been pregnant. There was no evidence or historical data to indicate the occurrence of an interstitial or ectopic pregnancy. Data bearing on the question of pregnancy were available in 148 patients, 21 years of age or over, who did not have tubal endometrium. There had been 109 with normal pregnancies varying from 1 to 12 in number, 1 set of twins, 37 abortions, usually spontaneous, 2 tubal pregnancies, 2 unable successfully to carry a pregnancy, and 39 who had never been pregnant. There was no significant difference between the two groups. Successful pregnancies occurred in 73.7 per cent of the first and 73.6 per cent of the second group. Abortions occurred in 38 and 34 per cent respectively. Pregnancies had not occurred in 26.3 and 26.4 per cent respectively. Whatever other sterility factors there may have been to raise the percentage of infertility from the population percentage of 15 per cent to 26 per cent in the cases from which the specimens were obtained for study, the presence of tubal endometrium appears to have played no appreciable role.

SUMMARY AND CONCLUSIONS

A report is presented of the observations made on the interstitial portion of the fallopian tubes of the uterus in 300 cases obtained from 259 hysterectomies and 41 autopsies. In all, 554 tubes were examined. The age incidence ranged from 4 months' intrauterine development to 87 years. The normal interstitial segment of the fallopian tube, measured from its junction with the cornual end of the extramural portion to its internal ostium at the funnel of the uterine cavity, is 1 centimeter or less in length. It has two components, a muscular coat and a mucosa. The muscular coat consists of an outer circular and an inner longitudinal layer. The outer layer is a continuation of the muscle of the extramural portion of the tube and soon becomes lost in the myometrium. The inner longitudinal layer is a continuation of the subendometrial muscle at the funnel of the endometrial cavity and becomes lost in the tubal muscle at its cornual end. The longitudinal muscular coat is very rich in vascular channels. An anatomic uterotubal sphincter is not demonstrable. Theoretically, the more developed inner longitudinal muscular coat may have a sphincteric action. The mucosa consists of a single layer of tall cylindrical cells in a villous pattern. Before puberty, it cannot be differentiated from the epithelium of the extramural tube and of the endometrium. It then usually assumes a tubal character but frequently is difficult to differentiate from the epithelium of the endometrium. The villous pattern varies from very simple to very complex and may differ within the tube itself and between right and left sides. Normal endometrium is present in the interstitial portion of the tube in approximately one-fourth of all uteri and may have a normal hormonal response. The presence of endometrium appears to be a normal developmental phenomenon and is not per se a pathologic condition. Its presence has no deleterious effect on the occurrence of

pregnancy. It has no definite causal relation to extrauterine endometriosis or salpingitis isthmica nodosa. Endometrial polyps are fairly frequent. Carcinomatous degeneration of these polyps has not been observed. One instance each of papilloma and of primary carcinoma arising from tubal epithelium is reported. Endometrial carcinoma of the uterine body may affect the interstitial tube by projection of a polypoid mass into its lumen, by spread along the surface, or by penetration into its vascular channels.

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VENOUS INVASION IN CARCINOMA OF THE RECTUM AS EVIDENCED BY VENOUS RADIOGRAPHY

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THE prognosis of patients with carcinoma of the rectum is adversely affected when venous invasion is present. Distant visceral metastasis usually takes place via the venous system, and can occur before lymph nodes are involved. The techniques utilized for establishing the presence of venous invasion generally have fallen into two categories, namely, gross dissection of veins and microscopic study of the latter by means of special stains. Yet venous invasion is not always demonstrated in the resected specimens of patients who undergo resection performed with the hope of cure but who later are found to have distant visceral metastasis. Hence, the conclusion is that these techniques, at best, do not give a true incidence of venous involvement. It was in the hope of identifying venous invasion more accurately that a new technique of outlining the venous system in the region involved by the carcinoma was undertaken. The technique, a modification of that originally described by Barringer, consists of injecting a radiopaque material into the venous system of the fresh surgical specimen, taking roentgenograms, and examining the areas of deformity and deficiency, both grossly and microscopically, for evidence of venous invasion by carcinoma.

Mode of entrance of carcinoma into veins, significance of venous invasion, and the fate of embolic malignant cells, have stimulated many experimental and clinical studies. Goldmann, in 1897, postulated that cancer cells enter the vascular coats via the vasa vasorum. Schmidt, in 1903, studied cases in which metastatic nodules were present in the lungs at necropsy and concluded that scattered embolization to the lungs occurs much more frequently than the development of gross metastasis. The emboli, which do not proliferate, either undergo intravascular destruction by thrombotic processes and leucocytic activity, or remain quiescent and sterile. The development of a vascular connection with the wall of the vessel was considered to be the determining factor for survival of transported neoplastic cells. Levin and Sittenfield postulated a specific affinity between the cancerous cells and cells of certain organs of the body, in explaining why metastasis was more prevalent at certain sites than at others, but this could not be confirmed by Iwasaki. Takahashi has given evidence of a specific property in certain neoplastic cells to produce irritation. Tyzzer, Marsh, and Knox demonstrated that massage of a tumor tends to increase the incidence of distant metastasis. Peristaltic action of the bowel produces constant massage of the tumor. This may explain why the prognosis is grave for patients having obstructive lesions as shown by Nickell and Dockerty.

Willis contended that abundant and constant metastasis results chiefly when the growth gains entry into a large vein. A tumor thrombosing a small vessel has little opportunity for embolic detachment of neoplastic fragments. However, as the thrombosing tumor extends intravascularly and as larger and larger vessels are entered, chances for separation of an embolus increase.

From the Mayo Foundation and the Divisions of Surgical Pathology and of Surgery, Mayo Clinic, Rochester, Minnesota.

Abridgment of thesis submitted by Dr. Madison to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

VENOUS INVASION AND METASTASIS

Site. Specimens of carcinomatous lesions of the rectum and sigmoid obtained at the time of resection and at necropsy have shown that venous invasion is found most commonly in the submucosal and perirectal veins. Submucosal venous invasion is identified by microscopic examination whereas perirectal in-

va ion often can be demonstrated grossly as w l.

he liver is the commonest site for distant vi eral metastasis from carcinoma of the rectu , and the lungs are the next commonest sit Brown and Warren found that in 170 ca s of rectal carcinoma, necropsy showed in lvement of the liver in 34 per cent and m stasis to the lungs in 22 per cent. Evide e of distant spread also was noted in the a nal glands, bones, thyroid glands, kidneys, in tines, and spleen. Bargen and Larson st ied resected specimens in 260 cases in w h metastasis or local extension had occu d and found involvement of the liver in 17 pe ent and metastasis to the lungs in 5 per ce

idence of venous invasion. The incidence of nous invasion associated with carcinoma of e rectum has been reported to be between 15 nd 61 per cent. The latter figure was repo d by Brown and Warren based on cases in hich necropsy had been performed. The inc lence in cases in which surgically resected sp imens were studied has ranged from 15 to 38 per cent, with Dukes (8) reporting 18 per cent, Grinnell (12) 36 per cent, Coller, Kay, and MacIntyre 15 per cent, Seefeld and Bargen 20 per cent, Sunderland 26.4 and 29 per cent, and Barringer 37.7 per cent.

The incidence of venous invasion increases with the degree of anaplasia according to Broders' method of grading and with the depth of penetration of the lesion and lymphatic extension, according to Dukes' (10) classification. Seefeld and Bargen found venous invasion in 7.1 per cent of all lesions of grade 1, 13 per cent of those of grade 2, 29.2 per cent of those of grade 3, and 62.5 per cent of those of grade 4. Grinnell (12) reported the incidence of venous invasion in each classification of Dukes as follows: 3.5 per cent in lesions of type A, 25 per cent in lesions of type B, and 49 per cent in lesions of type C.

Significance of venous invasion. Venous invasion implies serious prognosis for the patient. Brown and Warren stated that visceral metastasis is more accurately predicted by the presence of venous invasion than by the presence of neoplastic lymph nodes. In their series of cases necropsy revealed that only 1 of 70 cases of visceral invasion failed to show local intravascular invasion, whereas 24 per cent of cases with "negative" nodes had visceral metastasis. Dukes (9) studied 63 patients who suddenly died 1 to 2 weeks after undergoing resection of the rectum for carcinoma. Metastasis to the liver was found twice as frequently among the patients with venous invasion in the resected specimen as among those without venous invasion. Grinnell (12) found that of 82 patients without venous invasion, 76 per cent were alive 5 years after operation, whereas of 51 patients with venous invasion only 37 per cent survived 5 years after operation. Seefeld and Bargen

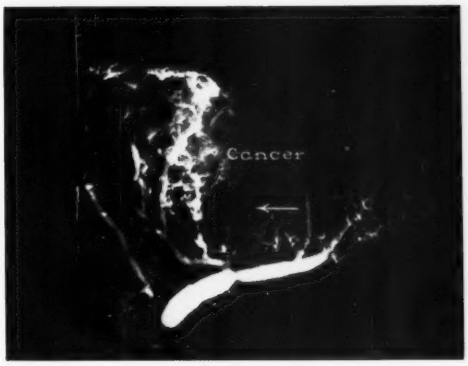


Fig. 1. Venous deficiency pattern showing a vein to the right and one leading to the left but no definite vein draining the carcinomatous region (arrow). Sections from this area of venous paucity showed microscopic venous invasion. The lesion was grade 1 (Broders') and type C (Dukes').

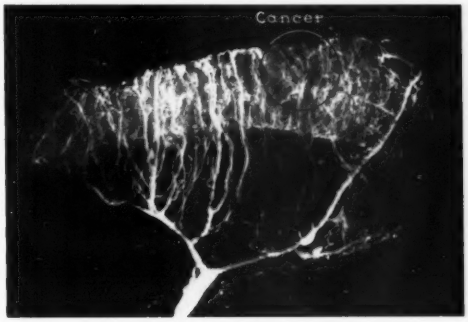
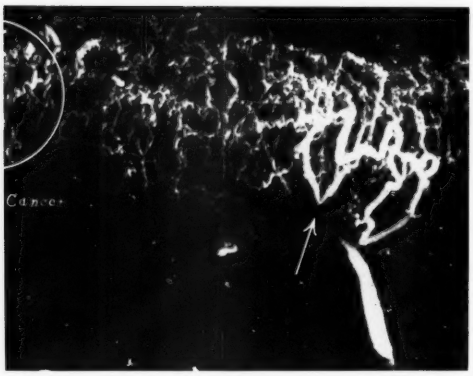


Fig. 2. Venous pattern without obstruction or deficiency of veins. Venous invasion was not found in microscopic sections. The lesion was grade 2 (Broders') and type B (Dukes').



a

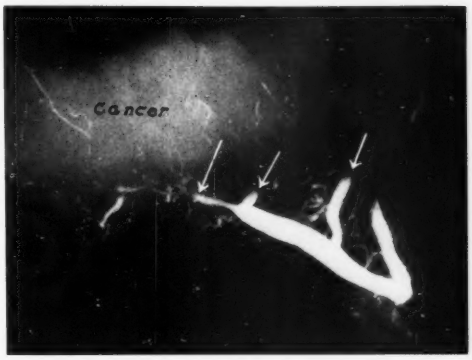
b

c

Fig. 3. a, Venous obstruction owing to an intravascular carcinoma is demonstrated in the main vessel (shown by arrow). The lesion was grade 2 (Broders') and type B (Dukes'). b, Hematoxylin and eosin stain, ×60. Note how difficult it is to demonstrate the venous wall using this type of stain. c, Van Gieson's elastic tissue stain of the same section as shown in b. Note the dark rim of elastica interna which identifies the vein. Several clumps of cancer cells can be seen scattered in the thrombus.

found visceral metastasis at operation or later in 94 per cent of cases when venous invasion was present in the primary growth. Visceral metastasis developed in only 18.7 per cent of the patients in whom venous invasion was absent. Sunderland found that if venous invasion was present as well as lymphatic involvement the prognosis was much poorer than when nodal involvement alone was present. The 5 year survival rate of patients having carcinoma of the rectum and sigmoid which involved lymph nodes and veins was only 20 per cent as compared to 57.7 per cent for those with nodal involvement only.

Relevant anatomic factors. The rectum begins anterior to the third sacral vertebra as a



a

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Fig. 4. a, Venous obstruction marked by arrows was due to carcinoma. The obstruction of the vein on the right was caused by a suture. Microscopic section of one of the veins invaded by carcinoma is shown in b and c. The lesion was grade 2 (Broders'), type C (Dukes'). b, Hematoxylin and eosin stain, ×30, of a vein with intraluminal carcinoma. Note thrombus formation. c, Same section as in b (van Gieson's elastic tissue stain, ×30). Note that the elastic tissue is more prominent when this stain is used.

continuation of the sigmoid, and ends at the pectinate line. According to Bacon, the average length of the rectum by proctosigmoidoscopic measurement is 13.5 centimeters. Buie's measurement of the anal canal varied in length from 1.5 to 3 centimeters, the average being about 2.5 centimeters. Its internal boundary is the pectinate line; the external boundary is the anal verge or the line where the walls of the anus come in contact with each other externally during the normal state of apposition. Proctosigmoidoscopic measurements in our study were read at the anal verge. Hence, if the so-called proctoscopic length of the rectum averaged 13.5 centimeters and the length of the anal canal averaged 2.5 centimeters, the

average distance of the rectosigmoid from the anal verge would be 16 centimeters. The lower borders of all lesions included in our study were proved by proctosigmoidoscopic examination to be 14 centimeters or less from the anal verge and the lesions were entirely above the pectinate line. We feel justified, therefore, in locating the lesions in the rectum.

Paired inferior and middle hemorrhoidal veins and the single superior hemorrhoidal vein provide venous drainage for the rectum. The superior hemorrhoidal vein is a tributary of the portal system, but the middle and inferior hemorrhoidal veins drain into the inferior vena cava. These anatomic facts are of great importance in venous spread of malignant disease.

MATERIALS AND METHODS

Specimens were obtained directly from the operating room and were studied prior to routine pathologic examination. All carcinomas of the rectum were used except those removed by posterior resection or two stage abdominoperineal procedure which proved unsatisfactory for venous injection. Our study included 42 carcinomas with lower margins between the pectinate line and a point 14 centimeters from the anal verge according to proctoscopic measurement.

The superior hemorrhoidal vein or one of its main tributaries was cannulated and irrigated with cold tap water. Major points of leakage were tied. The radiopaque material was light brominated olive oil (brominol) with enough methylene blue powder added to form a colored suspension. The mixture was then warmed in tap water to decrease its viscosity, and 10 to 20 cubic centimeters were injected into the venous system of the specimen. A sufficient amount was considered to be injected when the large veins remained distended and the distal capillaries contained methylene blue. The vein was then tied and the cannula removed. After injection the specimen was placed in cold water to increase the viscosity of the brominol and thus diminish any loss from the venous system through small venules which might be opened. A roentgenogram of the injected specimen was made and the wet plate was examined immediately. Two features were looked for: (1) venous obstruction and (2) a venous deficiency pattern between the vein and the lesion. A venous deficiency pattern refers to the absence or marked decrease in number of tributary veins between the lesion and the large veins draining the area (Fig. 1). A specimen without venous obstruction or deficiency is shown in Figure 2. Routine gross and microscopic examination of the specimen did not reveal venous invasion.

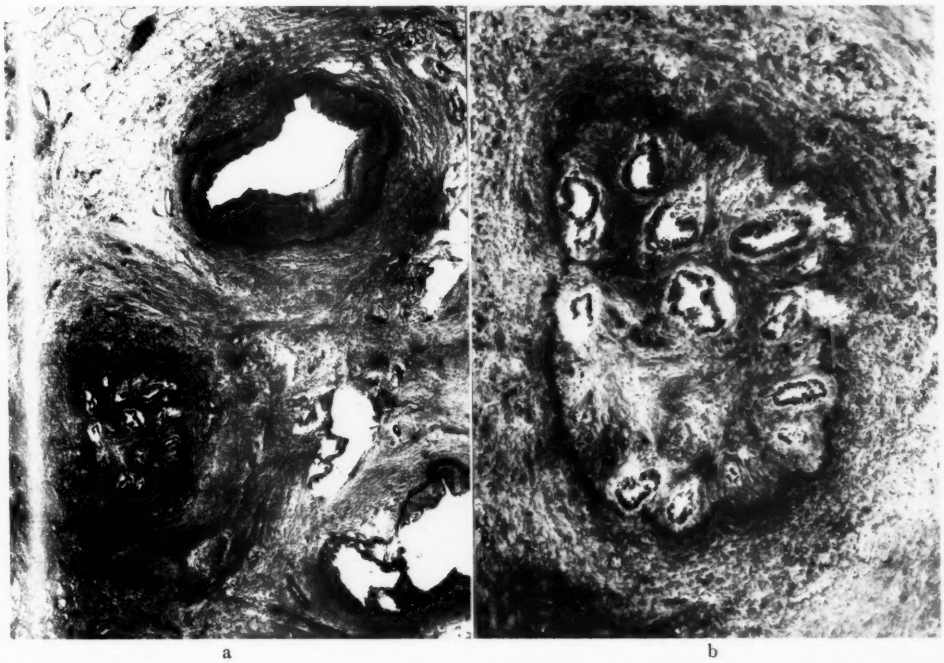
Points of obstruction, demonstrated roentgenographically, were examined for artefacts. The principal artefacts were ligatures, placed at the time of operation or during injection, and tension bands across the veins.

In Figure 3a obstruction of the main venous channel is demonstrated. Only 1 block, just proximal to the site of obstruction, was necessary to demonstrate intravenous carcinoma microscopically in a fresh frozen section stained with polychrome methylene blue. Permanent sections stained with hematoxylin and eosin, and van Gieson's stain for elastic tissue are shown in Figure 3b and c. Figure 4a shows several areas of obstruction, one of which was an artefact due to a ligature. Microscopic study of sections at the other sites of obstruction demonstrated intravenous carcinoma. One of these sections is shown in Figure 4b and c.

In our selection of blocks for microscopic examination we were guided by the roentgenograms; the total number of blocks from each specimen varied from 1 to 8. The specimen was considered positive for venous invasion if microscopic evidence of cancer cells was found within a vein and negative if not found after gross and microscopic search, regardless of the roentgenographic findings.

Fresh frozen sections stained with polychrome methylene blue were the best means of identifying veins, microscopically. This is well illustrated in Figure 5a and b. In Figure 5a the elastica interna and elastic tissue can be seen in the wall of the vein as well as in the artery. In fixed preparations the advantage of van Gieson's elastic tissue stain over hematoxylin and eosin stain is demonstrated (Figs. 3b and c and 4b and c).

Identification of veins in microscopic sections was made by utilizing histologic criteria.



a b

Fig. 5. a, Fresh frozen section stained with polychrome methylene blue. In the lower left is a vein containing carcinoma. Note the elastica interna and elastic tissue in the wall of the vein. An artery is included in the upper part of the photograph, demonstrating the prominent elastica interna and elastica externa (×21). b, Enlargement of the vein shown in a. Note definite carcinomatous cells in the vein and the well defined elastic tissue in the wall of the vein (×60).

Arteries possess thick muscular walls, definite internal elastic membranes, and small lumen to wall ratios, and it is not difficult to distinguish them from veins. Lymphatic vessels are sometimes difficult to distinguish from veins distended by thrombi. Lymphatics, however, have exceedingly thin layers of elastic and muscular tissues.

CRITERIA FOR IDENTIFYING VEINS

Ring of elastic tissue in wall of vessel. With the use of polychrome methylene blue stain or van Gieson's stain for elastic tissue a complete thick elastic membrane often could be seen (Figs. 3c and 5a and b). This seemed to be more characteristic of the medium-size vessels. The walls of the large veins had a more diffuse distribution of elastic tissue (Fig. 4c). Sometimes carcinoma destroys the continuity of the elastic tissue. One must be hesitant in identifying structures with incomplete and irregularly concentrated elastic tissue as veins because carcinoma protruding into surrounding structures may compress and concentrate elastic and fibrous tissues peripherally and cause them to mimic the appearance of the wall of a vein.

Thickness of vessel wall compared to size of lumen. Arteries have smaller lumens and the lymphatics have larger lumens than veins with the same mural thickness. Comparison of arterial walls with those of veins is seen in Figures 4c and 5a. Arteries and veins (except capillaries and small venules) have a muscular layer whereas only the larger lymphatics do.

Erythrocytes in lumen. Microscopic evidence of erythrocytes in the lumen is an aid in distinguishing blood vessels from lymphatics. This was of little value in this study since the veins had been irrigated.

TABLE I.—CLASSIFICATION OF VENOUS INVASION

Broders' method grade	Total cases	With venous invasion	
		No.	Per cent
1	11	3	27.3
2	23	10	43.5
3	8	5	62.5
4	0	0	–
Total	42	18	42.9
Dukes' classification type			
A	1	0	0
B	19	6	31.6
C	22	12	54.5
Total	42	18	42.9

The technique described differed from that of Barringer in minor details. One difference was that only lateral roentgenographic views of the specimen were taken since it was soon discovered that stereoscopic and anteroposterior views were of no advantage. Methylene blue powder was easier to use than an aqueous solution of the dye and gave better indication of the peripheral extent of venous filling. The main difference in interpretation was that a deficiency type of pattern was found frequently. This was considered as venous obstruction between the carcinoma and the main venous channel.

RESULTS

In 18 of the 42 specimens, or 42.9 per cent, venous invasion by carcinoma was demonstrated microscopically. Of the 42 patients 4 had palpable metastatic nodules in the liver, 1 patient had omental transplants, and 2 others exhibited peritoneal invasion. Operations on these 7 patients were considered to be palliative resections and all 7 patients had venous invasion. The remaining 35 patients had undergone resections designed to cure. Eleven or 31.4 per cent of the 35 were found to have venous invasion by carcinoma.

TABLE II.—INCIDENCE OF VENOUS INVASION DETERMINED BY PROCTOSCOPIC MEASUREMENTS

Distance of lesion from anal verge, cm.	No. with venous invasion	No. without venous invasion	Total
3– 5	1	2	3
6– 8	5	7	12
9–11	4	9	13
12–14	8	6	14

Roentgenograms of 15 (83 per cent) of the 18 specimens in which the presence of venous invasion was subsequently proved microscopically, showed venous obstruction or a venous deficiency pattern. In 10, the roentgenograms indicated the obstructive pattern and in 5 the deficiency pattern. Two roentgenograms did not show venous obstruction or a deficiency pattern. In 1 of these 2, veins could not be identified microscopically because of an extensive mucous carcinoma although arteries could be seen readily. It was felt that venous invasion probably was present but that the carcinoma had destroyed the veins beyond recognition. The other roentgenogram had adequate filling of the veins. A third roentgenogram was unsatisfactory owing to technical difficulties.

Of the 24 specimens which did not show microscopic evidence of venous invasion, 21 (87 per cent) had no roentgenologic evidence of obstruction or deficiency but 3 did show such evidence. Two roentgenograms were classified as unsatisfactory and were included in the negative groups. Of the 3 roentgenograms showing "false" positive evidence, 2 showed evidence of the obstructive and 1 of the deficiency pattern type.

Results of our study agreed with those mentioned earlier in that incidence of venous invasion increased with the grade of the lesion according to Broders' method of grading and also according to Dukes' method of classification (Table I). The incidence of venous invasion at different proctoscopic levels as measured from the anal verge is given in Table II. Although this series is not large enough to warrant any definite conclusions, the incidence of venous invasion increased directly with the distance of the lesion from the anal verge. This differs from the studies of Sunderland who found venous invasion most frequent in the lowest 6 centimeters of the rectum.

Table III shows the distribution of lesions according to the ages of the patients. Carci-

noma of the rectum and rectosigmoid was most prevalent among patients in the seventh decade of life and venous invasion also was present more frequently in that age group. Of the 42 patients, 29 were men and 13 women. Of the 18 patients with venous invasion, 12 were men and 6 were women.

TABLE III.—DISTRIBUTION OF LESIONS ACCORDING TO AGE OF PATIENT

Age of patient, years	No. with veins involved	No. without veins involved	Total
30–39	1	1	2
40–49	2	7	9
50–59	3	5	8
60–69	10	7	17
70–79	2	4	6

COMMENT

Most 5 year survival rates for carcinoma of the rectum, excluding hospital mortality and palliative resection, have been reported to be between 45 and 65 per cent. These rates have not improved appreciably over the past 30 years despite a higher resectability rate and a lower operative mortality rate as shown by several studies. Grinnell (13) reported that the resectability rate for rectal carcinoma in his institution rose from 65.7 per cent for the period from 1916 to 1920 inclusive, to 83.3 per cent from 1945 to 1950 inclusive, and the operative mortality rate fell from 40.9 per cent to 6.7 per cent over the same period. The 5 year survival rates of patients who survived operation, on the other hand, were 50 per cent for periods from 1916 through 1930, 64.2 per cent for 1931 through 1935, 68.5 per cent for 1936 through 1940, and 45.6 per cent for 1941 through 1945.

Rankin and Broders reported 41.26 per cent good results; that is, the patient had been free from cancer, as far as it could be ascertained, in 521 resections for carcinoma of the rectum performed at the Mayo Clinic in the period from 1916 through 1925. Waugh and Kirklin reported a 5 year survival rate of 53 per cent for 255 cases in which abdominoperineal resection was performed during 1931 through 1940 at the same institution. Mayo reported a hospital mortality rate for one stage abdominoperineal resections for 1920 through 1929 of 27.7 per cent and for 1940 through 1948 of 3.6 per cent.

Several factors undoubtedly have prevented any remarkable improvement in the survival rate. Venous spread is one of the factors. At the time of this report there is no method which will demonstrate distant venous metastasis if the results of clinical studies and surgical exploration are negative. It has been shown, however, that the prognosis of a patient is worse when venous invasion is present in a resected specimen, than when it is not present. Sunderland, for instance, found that the 5 year survival rate was almost three times higher when lymphatic involvement only was present, than when lymphatic and venous invasion were coexistent. The prediction of venous metastasis can be based on venous invasion in the resected specimen. We had hoped to locate venous invasion more accurately with the use of the venous injection technique.

The rate of incidence of venous invasion in our series of surgically resected specimens was 42.9 per cent. Excluding the cases in which palliative resection was performed, the incidence was 31.4 per cent. Barringer used a similar technique, and reported venous invasion in 37.7 per cent of his cases of carcinoma of the colon and rectum. Excluding cases of palliative resection, his incidence was 33.3 per cent. Hence it must be assumed from these two studies that the addition of the venous injection technique to gross studies and microscopic search has helped in locating and identifying venous invasion. The venous injection technique is not intended to replace the routine method of searching for venous invasion but to act as a supplementary aid. As yet it is too difficult a technique to be used other than in investigative work. Further study may produce a technique which is simpler and which will be applicable to all resected specimens.

It will be of great importance to follow the patients in this series, and to compare the 5 year survival rates of those having venous invasion with the rates of those without such invasion. In this way only can the seriousness of venous invasion be evaluated.

SUMMARY AND CONCLUSIONS

Venous invasion in a surgically resected specimen of carcinoma of the rectum gives a poor prognosis for the patient. A new venous injection technique for locating venous invasion proved to be helpful. This technique is not intended to replace gross and microscopic searches for venous invasion, but merely to facilitate such searches by localizing the zones of vascular narrowing. Tissue blocks taken from such areas reveal the highest incidence of malignant vascular invasion.

With the aid of this injection technique the incidence of venous invasion proved microscopically was found to be 42.9 per cent in 42 carcinomas of the rectum. With the exclusion of palliative resections, the incidence was found to be 31.4 per cent among patients on whom resection was performed with hope of cure.

Roentgenograms revealed venous obstruction or deficiency in 83 per cent of the cases with proved microscopic invasion and such obstruction or deficiency was absent in 87 per cent of cases which did not show microscopic evidence of venous invasion.

The incidence of venous invasion in this study increased with the grade of the lesion according to Broders' method of grading, with the depth of penetration and lymphatic extension of the lesion according to Dukes' classification and also as the level of the rectosigmoid was approached from the pectinate line.

The best and quickest method of identifying venous invasion is by the use of fresh frozen sections stained with polychrome methylene blue. Van Gieson's stain for elastic tissue is the best means of identifying venous invasion in fixed preparations.

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SOME FACTORS OTHER THAN NEOPLASMS ALTERING THE PROSTATIC FRACTION OF ACID PHOSPHATASE IN THE SERUM

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THE correlation between elevated values of serum acid phosphatase and carcinoma of the prostate is well known. It has been established, however, that determination of the enzyme is limited as a diagnostic procedure in prostatic cancer since in a significant number of patients at advanced stages of the disease the values are normal.

Elevations of serum acid phosphatase have been reported to follow manipulation of the prostate gland. In 4 of 20 patients studied by Hock and his associate, the values (measured in Bodansky units) were elevated after prostatic massage; in 4 others, the values were borderline. Daniel and his associate found that in 3 of 24 patients with benign prostatic hypertrophy there was a rise in serum acid phosphatase levels (measured in King-Armstrong units) after manipulation of the prostate. On biopsy, elevations were attributed to cystic degeneration of the prostate.

Since the introduction by Fishman and Lerner (3) of a technique for measuring the prostatic fraction of the serum acid phosphatase by *L*-tartrate inhibition and the report of its diagnostic significance in prostatic cancer (2), this laboratory has investigated some of the common situations that may raise the serum concentration of this enzyme into the abnormal range.

METHOD

Thirty male patients in a chronic disease hospital were chosen for study. These included 22 subjects without malignant disease of the prostate, so far as could be determined clinically, 5 whose (benign) prostate glands had presumably been completely removed by surgery, and 3 who were receiving estrogen therapy for proved advanced metastatic carcinoma of the prostate.

After an initial control venous blood was drawn, the prostate gland (prostate area in the prostatectomized patients) was massaged for 2 minutes. Additional blood specimens were then drawn at ½ hour, 1 hour, and 2 hour intervals after the manipulation.

Fourteen subjects received 100 milligrams of testosterone intramuscularly daily for 10 days. Twelve received 50 milligrams of testosterone intramuscularly daily for 10 days, and 4 of this group subsequently received a 10 day course of testosterone at the 100 milligram daily level. Blood samples were drawn before and after therapy in all cases.

Blood samples were also drawn from 4 patients before and after a warm enema had been given.

All determinations were carried out as outlined by Fishman and Lerner (3).

RESULTS

The normal range of total serum acid phosphatase is considered to be from 0.5 to 5.0 King-Armstrong (K.A.) units per 100 milliliters of serum. The normal range for the serum prostatic phosphatase is at present considered to be from 0.0 to 0.5 K.A. unit.

Effects of prostatic massage. As might be expected, in the 5 patients without prostate glands neither the total nor the prostatic fraction of the acid phosphatase was elevated into the abnormal range (Chart 1).

The values measured in the 3 patients with carcinoma of the prostate reflected the sever-

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Dr. Bonner is a Trainee of the National Cancer Institute.

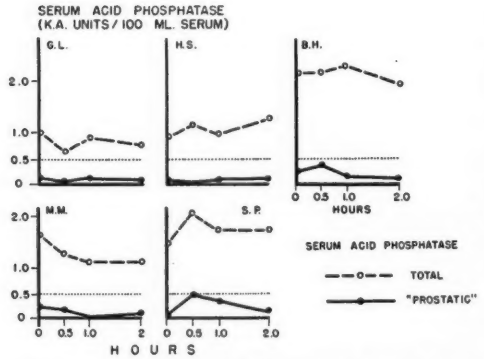

Chart 1. Total and prostatic serum acid phosphatase values before and after massage of the prostate area in patients whose (benign) prostate glands had presumably been completely removed by surgery. The higher prostatic values may be due to residual prostatic tissue or may represent minimal values for acid phosphatase from the liver and spleen, which may also be inhibited by *L*-tartrate.

ity of the disease (Chart 2). One patient (L.A.) had an initial total acid phosphatase value of 40.0 K.A. units and a prostatic value of 37.0 K.A. units, which rose to 46.0 and 42.0 units respectively at the half hour interval. He had a rapid downhill course and expired in spite of therapy.

The second patient in this group (A.G.) had revealed an initial total serum acid phosphatase level of 5.4 K.A. units and a prostatic fraction of 5.2 K.A. units. A half hour after massage these values rose to 7.4 and 6.4 K.A. units respectively. This patient is still living but has had a stormy hospital course necessitating a bed-and-chair existence.

The third patient in this group (J.N.) had an initial total serum acid phosphatase level of 1.2 K.A. units and a prostatic fraction of 0.2 K.A. units. There was no significant rise in either determination. This patient is clinically well, without pain, and enjoys a good appetite and an excellent state of nutrition.

All 3 of these patients had advanced metastatic disease and were receiving maximal estrogen therapy.

The 22 patients without clinical evidence of malignant disease of the prostate divided themselves into two groups. In 10, one of whom (B.K.) had a total of 3 prostatic massages, neither the total serum acid phosphatase nor the prostatic fraction rose into the abnormal range after prostatic massage (Chart 3). In the other 12 of the 22 patients who presumably showed no evidence of malignant disease, the prostatic fraction of the serum acid phosphatase rose into the abnormal range after prostatic massage (Chart 4). One patient (H.C.) also had an abnormal total serum acid phosphatase value, which was extremely elevated after the first prostatic massage, just under abnormal after a second massage, and again in the abnormal range after a third massage; the values for the prostatic fraction closely paralleled those for the total acid phosphatase (Chart 5). Two other subjects in this group (L.R. and H.Y.) received a second prostatic massage with a reduplication of results being seen in each. One patient demonstrated an elevated prostatic fraction after one massage but no rise after a second manipulation.

Effects of testosterone administration. In 3 of the 14 patients receiving a single course of 100 milligrams of testosterone daily for 10 days the value of the prostatic fraction was elevated to 0.6, 0.8, and 0.9 K.A. unit after the course of therapy. The total serum acid phosphatase level was 2.1 K.A. units in each.

Chart 2. Total and prostatic serum acid phosphatase values before and after massage of the prostate gland in 3 patients with carcinoma of the prostate.

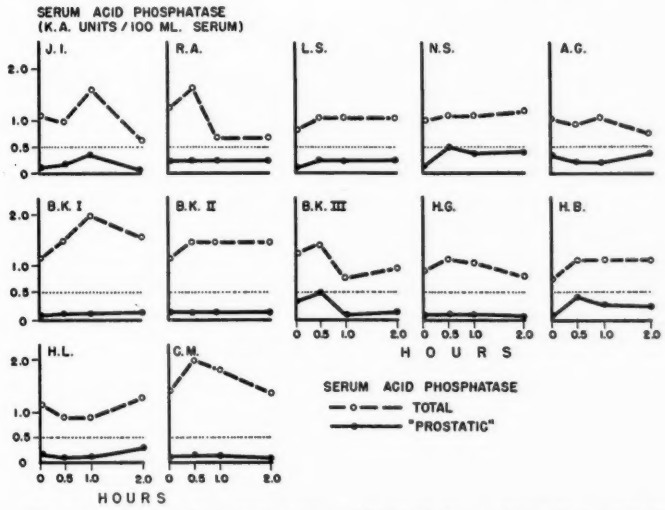

Chart 3. Total and prostatic serum acid phosphatase values after prostatic massage in 10 of the 22 patients who showed no clinical evidence of malignant prostatic disease. Massage failed to stimulate any increase of the prostatic values into the abnormal range.

In the 12 patients receiving 50 milligrams of testosterone for 10 days there was no elevation in either the total or the prostatic serum acid phosphatase, a negative finding which was seen in 4 of these subjects receiving an additional course of 100 milligrams of testosterone daily for 10 days.

Effects of enemas. Enemas produced no rise to abnormal values of serum acid phosphatase.

DISCUSSION

The elevated total serum acid phosphatase in patients who have carcinoma of the prostate consists almost entirely of *L*-tartrate inhibited phosphatase. The increase in the total value after prostatic massage, and in some instances after testosterone administration, is due to the increase in the prostatic fraction practically unit for unit. As used in this paper the Fishman-Lerner technique appears, therefore, to measure acid phosphatase originating in the prostate.

Sources other than the prostate may be responsible for *L*-tartrate inhibited phosphatase in those patients who after prostatectomy still have minute amounts of this enzyme in the serum. In 2 of 5 such patients prostatic massage increased the serum acid phosphatase which may be interpreted as arising from remnants of incompletely excised prostatic tissue (Chart 1). This fraction fluctuates little, and the amount seen in the prostatectomized patients may have come from the liver or spleen, if not from residual prostate tissue.

The rise in total serum acid phosphatase to 33.8 K.A units per 100 milliliters (prostatic 30.8 K.A. units) in 1 patient suggests the rupture of a large cyst in a cystic prostate, such as reported by Daniel and Van Zyl. It might be hypothesized that in the group in whom the prostatic fraction was elevated after massage the prostate gland is of a cellular and cystic pattern, and that in the group in whom there was no elevation the prostate is probably more fibrous in character. Clinically, no definite distinction could be made by palpation, and the matter remains a problem to be investigated.

In 1 of our 22 patients the total serum acid phosphatase increased to an abnormal level after prostatic massage; whereas in 12, including this one, the prostatic fraction rose into the abnormal range. Three of the 18

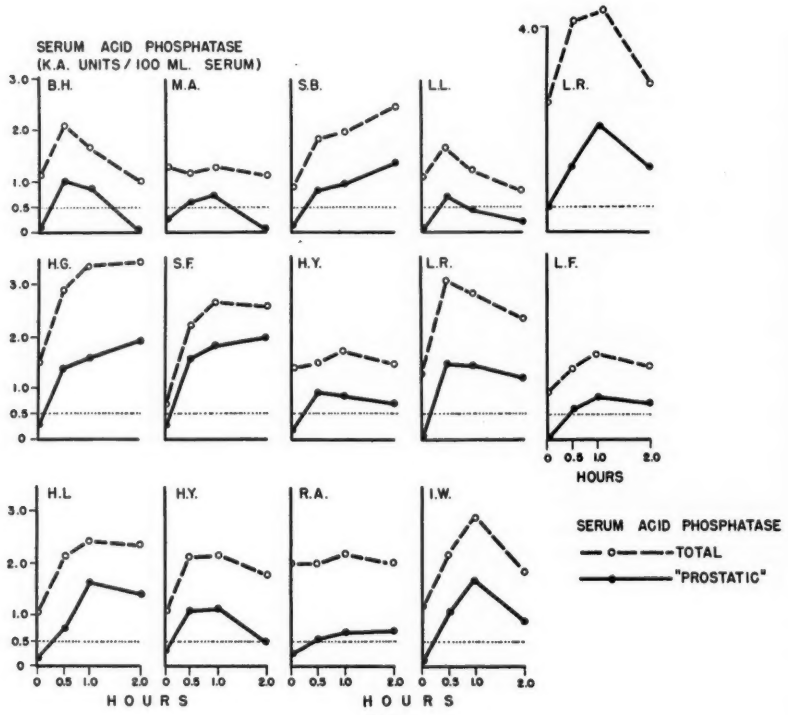

Chart 4.

Chart 4. Total and prostatic serum acid phosphatase values in 12 patients whose prostatic values all increased into the abnormal range after mechanical prostatic stimulation. These patients were in the group of 22 who presumably showed no clinical evidence of malignant disease.

Chart 5. Total and prostatic serum acid phosphatase values after 3 prostatic massages in a patient. The large increase in the prostatic fraction after the first massage may have been caused by the rupturing of a cyst.

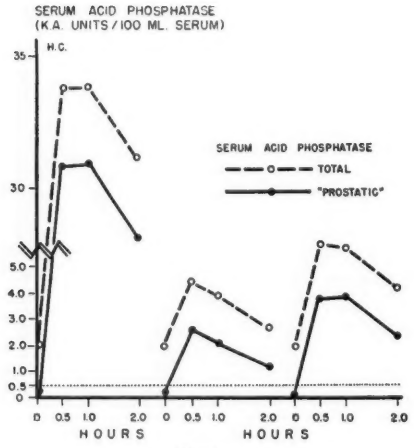

Chart 5.

subjects who received 100 milligrams of testosterone daily also had an elevated prostatic fraction (0.6, 0.8, and 0.9). In view of the sensitivity of the measurement obtained by the method of Fishman and Lerner, elevated values of prostatic serum acid phosphatase determined by this method after prostatic manipulation or testosterone therapy must be interpreted with caution. If a prostatic cancer is suspected, this test should, therefore, be performed prior to, if possible, or at least 2 days after prostatic manipulation, and after withholding testosterone therapy for at least 1 week.

SUMMARY

1. Total serum acid phosphatase and prostatic serum acid phosphatase levels were determined in 30 patients before, and ½ hour, 1 hour, and 2 hours after a 2 minute massage of the prostate or prostate area. Twenty-two patients had no demonstrable malignant disease of the prostate, 5 had no prostates, and 3 had proved carcinoma of the prostate treated by estrogens.

2. There was no abnormal elevation of the enzyme in the 5 prostatectomized patients, in 10 of 22 patients with nonmalignant prostate glands, and in 4 patients studied after they were given enemas.

3. An elevation of the prostatic serum acid phosphatase into the abnormal range appeared in 12 of the 22 patients with nonmalignant prostate glands. Only 1 of these patients with a nonmalignant prostate gland concomitantly showed an abnormal elevation of the total serum acid phosphatase.

4. The prostatic fraction was elevated into the abnormal range in 3 of 18 patients after a 10 day course of 100 milligrams of testosterone daily.

5. When the sensitive Fishman-Lerner technique of measurement is used, caution is advised in interpreting elevated values of prostatic serum acid phosphatase obtained after prostatic manipulation or testosterone therapy.

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AN INTERIM NOTE ON THE APPLICATION OF THE SKIN BIOPSY TEST OF CHROMOSOMAL SEX TO HERMAPHRODITES

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IN previous reports the writer and his coworkers have shown that there is a difference in nuclear structure, according to sex, in cells of many tissues of various species, including man (1, 3, 6, 7). In brief, intermitotic nuclei of females contain a special mass of chromatin, the sex chromatin, which is encountered rarely in nuclei of males. The sex chromatin of females is usually located against the inner surface of the nuclear membrane, where it forms a planoconvex mass just under 1 micron in diameter.

Certain regions of chromosomes are more likely than others to remain compact in the intermitotic nucleus. They are said to behave in a heteropyknotic or heterochromatic manner and produce chromatin particles of variable size. In general, the property of heteropyknosis is enhanced in the sex chromosomes, compared with the remaining chromosomes or autosomes. Although the evidence is of an indirect nature, it seems likely that the sex chromatin of female nuclei is formed by the fusion of heteropyknotic portions of the two X chromosomes. If this is so, it follows that the XY sex chromosome complex of males does not form a mass of chromatin which is comparable in size with that produced by the XX sex chromosomes of females. The small size of the Y chromosome may be partially responsible for the characteristic structure of intermitotic male nuclei.

All who are concerned with the complex problem of hermaphroditism feel the need for some method of detecting the type of sex chromosome complex in these difficult cases. One procedure is to examine the chromosomes during meiosis in male germ cells. Hsu, Hooks, and Pomerat have recently applied an interesting modification of the tissue culture technique to this problem. Although these methods are most valuable, their application is restricted because the techniques are difficult and can be used effectively only by cytologists with specialized training.

The study of epidermal nuclei in a skin biopsy offers a relatively simple method of inferring whether the sex chromosomes are of the XX or XY variety. Routine staining procedures (hematoxylin and eosin, Feulgen) are satisfactory, although the preparations must be of excellent quality technically. The examination of the tissue can be carried out by any experienced microscopist. Moore, Graham, and Barr reported the results of skin biopsy tests of chromosomal sex in 2 cases of pseudohermaphroditism. One patient (female pseudohermaphrodite with adrenogenital syndrome) had female type nuclei; the second patient (a male pseudohermaphrodite) had male type nuclei. We have since had the opportunity of studying skin biopsies from 27 patients. A detailed account of this work will appear at a later date. This brief interim report has been prepared in the hope that the observations will be helpful to physicians who may be applying the skin biopsy test of chromosomal sex to isolated cases.

OBSERVATIONS

In recording the observations, the terminology of the Klebs classification, which is based primarily on the nature of the gonads, will be used for the clinical diagnosis. True hermaphrodites have both ovarian and testicular tissue. In male pseudohermaphrodites the gonads are testes, and in female pseudohermaphrodites the gonads are ovaries. The great majority of female pseudohermaphrodites belong to the congenital adrenogenital syndrome and are caused by hyperplasia of

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the fetal adrenal cortex. They form a fairly homogeneous group, anatomically. The most common features in untreated cases are enlargement of the clitoris, maldevelopment of the vaginal canal, masculine body build, hirsuties, skeletal age in advance of the chronologic age, and elevated urinary 17-ketosteroids. A uterus, tubes, and ovaries are present, although they may be smaller than normal and the ovaries often show some cystic degeneration. In the other types of hermaphroditism, there is a great variation in the anatomy of the internal and external genitalia, and in the secondary sex characteristics.

The ages of the patients varied between 1 week and 68 years, with an average age of 16 years. Of the total of 29 patients, the epidermal nuclei were similar to those of normal females in 16 subjects, and similar to those of normal males in 13 subjects. The relation between nuclear morphology and clinical diagnosis is as follows: (a) 4 true hermaphrodites, 3 with female type nuclei and 1 with male type nuclei; (b) 14 female pseudohermaphrodites, 12 belonging to the adrenogenital syndrome and with female type nuclei and 2 not belonging to the adrenogenital syndrome, 1 with female type nuclei and 1 with male type nuclei; (c) 11 male pseudohermaphrodites all with male type nuclei.

Any generalizations which are made at this time will undoubtedly require modification as additional patients become available for study. Nevertheless, the results suggest that true hermaphrodites, and female pseudohermaphrodites which are the result of factors other than adrenal cortical hyperplasia, may have either female type or male type nuclei. Both of these varieties of hermaphroditism are relatively rare. On the other hand, cases of female pseudohermaphroditism, caused by adrenal cortical hyperplasia, and cases of male pseudohermaphroditism are consistent in this small series in having female type nuclei and male type nuclei, respectively.

DISCUSSION

From an analogy with the nuclear morphology of normal females and males, it may seem quite safe to infer that hermaphrodites with female type nuclei have XX sex chromosomes and that those with male type nuclei have XY sex chromosomes. Although it is likely that such an inference is usually valid, it may not apply in every case. For example, it is theoretically possible that nuclei containing an XXY complex would be similar in appearance to those of normal females. There is also the possibility that nuclei containing an X, but no Y, chromosome, or even no sex chromosomes at all, would present the morphology of normal male nuclei. It should be possible to clarify this matter with the technique of tissue culture which Hsu, Hooks, and Pomerat are using. Until observations to the contrary appear, it will be assumed that hermaphrodites with female type nuclei have the XX sex chromosome complex, and that those with male type nuclei have XY sex chromosomes.

This study has an important bearing on the theoretic background of hermaphroditism. For example, the view that these patients in general bear the XX sex chromosome complex is frequently encountered. This belief seems to be based largely on the meticulous work of Goldschmidt on intersexuality in the gypsy moth. The transference of this work on insects to anomalies of sex development in mammals may have been encouraged by Lillie's classical work on the freemartin, by studies on the adrenogenital syndrome, and by the experimental observation that it is easier to transform ovaries into testes than to effect a change in the reverse direction. The present observations seem to rule out such a generalization. Female pseudohermaphrodites caused by hyperplasia of the fetal adrenal cortex are a special type of maldevelopment and the only one for which much is known with respect to etiology. If the 12 cases in the present series which belong to this group are set to one side, there remain 17 patients, of whom 13 have male type nuclei. Wilkins reserves the term "intersex" for cases of hermaphroditism in which no evidence of adrenal pathology can be demonstrated. Their etiology is unknown but genetic factors are undoubtedly important, with the possibility that there is some unrecognized hormonal disturbance of maternal or fetal origin. In any case, it appears that within the extremely varied intersex group it

is an embryo with the XY sex chromosome constitution which is the more unstable with respect to sex development. The same conclusion was reached by Pettersson and Bonnier on the basis of a genetic analysis of families containing several intersex individuals. The chief value of the skin biopsy test in practice seems to be in differential diagnosis between the two most common types of hermaphroditism, the adrenogenital syndrome and male pseudohermaphroditism, when such clinical tests as the output of 17-ketosteroids and skeletal age are equivocal. It is now more important than ever before to recognize the adrenogenital patients early, since they are benefited so much by cortisone. The rare conditions of true hermaphroditism and female pseudohermaphroditism of the intersex type must be borne in mind whether the epidermal nuclei correspond with those of normal females or normal males. Should this technique become widely accepted, it may be that it will provide sufficient additional information in certain cases so that an exploratory laparotomy will not be thought necessary.

A proportion of male pseudohermaphrodites have strongly female characteristics, anatomically and psychologically, and they are more suited to life as females. At the outset of these nuclear studies, it was hoped that the epidermal nuclei of such patients might have a female morphology. In such an event, the skin biopsy test would give a better indication of the dominant sex, taking all aspects of the case into consideration, than the nature of the gonads. This hope has not been realized. Two of the male pseudohermaphrodites in the present series have external genitalia which would be considered normal, or nearly so, for a female. Such patients should undoubtedly be treated as females, regardless of their male gonads and male type nuclei. The results which are being obtained with cortisone in adrenogenital cases give promise that these patients can be orientated successfully toward life in the female role, in accordance with the anatomy of their internal genitalia and the female structure of their nuclei. For the intersex patients the decision as to the wisest course of action remains a matter of clinical judgment based on all available data. It is desired to stress this point, in order that no one will be tempted to extend the results of the skin biopsy test into practice literally, where other considerations make such a course of action inadvisable.

SUMMARY

The skin biopsy test of chromosomal sex has been applied to 29 cases of hermaphroditism; 16 patients had female type nuclei and 13 patients had male type nuclei. This preliminary study indicates that the skin biopsy test is a useful aid in the differential diagnosis between the congenital adrenogenital syndrome and male pseudohermaphroditism when the clinical findings are equivocal.

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THE ALTERED RESPONSE TO SODIUM LOADING IN SEVERAL SEVERELY BURNED INDIVIDUALS AFTER INITIAL TREATMENT WITH HYPERTONIC SODIUM CONTAINING FLUIDS

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FOLLOWING a severe trauma it is generally recognized that a varying period of salt retention is encountered. The reason for this has been ascribed mainly to the increase in adrenal activity, although some have thought that the hyponatremia following trauma might be a contributing, or even the only factor. The reason that increased adrenal activity is held responsible for the sodium retention arises from the knowledge that stress is accompanied by an increase in the production of adrenocorticotrophic hormone (ACTH) together with the fact that some adrenal hormones are powerful sodium retainers. However, the effect of ACTH as well as cortisone and desoxycorticosterone acetate (DCA) on sodium metabolism has to be qualified since it is often only transitory and, under certain conditions, reversed. Patients with Cushing's syndrome, for instance, respond to a sodium load with a urinary sodium excretion which is higher than that of a normal person. Thus, it cannot be taken for granted that a patient, following a severe stress, will necessarily retain sodium because of an increased adrenal activity.

Trauma, due to major operations and burns, has been shown by several investigators to cause a consistent depression of serum sodium. Lowering of the serum sodium is usually accompanied by a lack of ability to handle water, resulting in days of edema, oliguria, or even anuria. By restoring the serum sodium to the pretraumatic level, one should be able to evaluate whether the posttraumatic sodium retention is a necessary result of increased adrenal activity or merely due to the lowered serum sodium.

The restoration of serum sodium in a patient with oliguria can only be accomplished by the administration of sodium in excess of the concentration in the serum, since one otherwise would just expand the extracellular fluid. For this study we have chosen 3 severely burned children to whom hypertonic sodium chloride was given intravenously until, by our criteria, we believed that the serum sodium had been restored. This study deals with the ability of these children to handle a sodium chloride load in the early stages of this condition of severe stress.

MATERIAL AND METHODS

The electrolyte and water disturbances in 3 severely burned children were treated according to the principles outlined in previous publications (2, 3).

A Foley catheter was inserted into the bladder of the patients immediately following admission and output, urinary *p*H, and electrolytes were continually followed on an hourly basis for several days. Twelve to 18 hours following the burn, during which time adequate hydration was attempted, hypertonic sodium chloride solutions were infused intravenously in amounts which were calculated to increase their serum sodium approximately 5 to 10 milliequivalents per liter. This would, in most cases, result in a normal pattern of urinary *p*H fluctuation. In the cases in which this was not obtained nor maintained, additional hypertonic sodium chloride was given.

The ability of the patients to excrete sodium following a sodium load was evaluated by cal-

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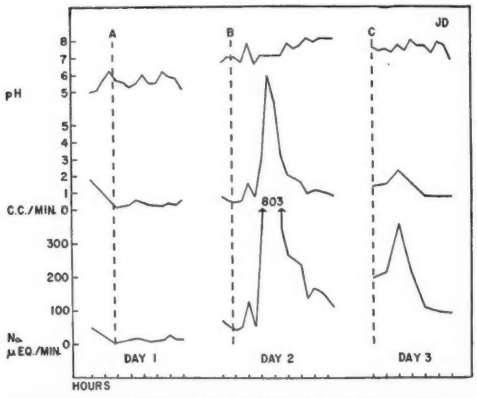

Fig. 1. The effect of the infusion of hypertonic sodium chloride on urinary *p*H, water diuresis, and sodium excretion in a severely burned child (J.D.). The infusions were given at the times indicated by the dotted lines which cross the curves and were administered on 3 successive days.

culating the percentage return of each load (Figs. 2, 4, and 6).

Since this paper only deals with the electrolyte disturbances in the early phase of a burn, the case histories merely outline the initial treatment until the start of hypertonic sodium infusions.

CASE REPORTS

J.D., (G.H.), an 8 year old male, was admitted to the hospital 30 minutes following a severe burn. Thirty-seven per cent of the total body area was involved with third degree burns, and an additional 20 per cent of the body and face was involved with first and second degree burns. The tongue and pharynx were involved with first degree burns. Oxygen was started by nasal catheter. Local therapy involved irrigation of the involved areas with normal saline, and furacin gauze strips were applied with pressure dressings. Adequate doses of both aqueous and procaine penicillin were administered as well as 3,000 units of tetanus antitoxin. Intravenous therapy consisted of 750 cubic centimeters of

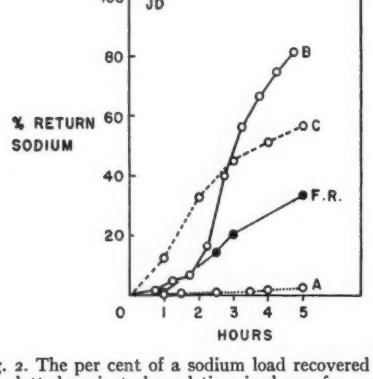

Fig. 2. The per cent of a sodium load recovered in the urine plotted against elapsed time is shown for a normal subject (*F.R.*) and a severely burned child (*J.D.*) (curves *A*, *B*, and *C*).

TABLE I.—BLOOD CHEMISTRY STUDIES

Patient J.D.					
Day of hospitalization	mEq./L.				Mgm. per cent N.P.N.
	Na	K	Cl	CO_2	
1, 6 hr. after admission	130	6.3	90	21	
2, A.M.	143	5.6	100	17	71
P.M.	132	5.0	112	19	53
3, A.M.	136	6.2	102	22	56
P.M.	134	6.4	110	18	59
4, A.M.	135	4.4	106	22	50
P.M.	135	4.1	103	20	45
5, A.M.	135	4.0	103	20	45
P.M.	140	4.0	108	28	37
6, A.M.	135	4.7	116	29	33
P.M.	136	4.6	109	27	39
7	135	4.2	102	21	38
8	132	4.3	110	20	41
9	136	4.3	113	23	34
10	135	4.6	104	20	45
Patient S.M. 1, Admission	146	4.0	109	13	
8 hr. after admission	138	4.8	106	22	
2, A.M.	140	5.5	114	16	25
P.M.	140	5.3	111	26	
3, A.M.	139	4.6	102	23	
P.M.	140	4.7	107		
4, A.M.	136	5.1	110	19	20
P.M.	138	5.0	106	23	
5, A.M.	143	5.0	105	22	15
P.M.	135	4.8	103	22	
6, A.M.	141	4.5	112	21	16
P.M.	140	4.8	110	22	
7	137	4.8	106	19	20
8	135	4.5	107	18	20
9	140	5.0	106	14	18
10	150	4.4	105		24

plasma, 1,000 cubic centimeters of isotonic saline, and 1,000 cubic centimeters of 5 per cent dextrose in water administered during the first 12 hours of hospitalization. A Foley catheter was inserted for accurate fluid output studies. Some of the blood chemistry studies for the first 10 days of the hospital stay are recorded in Table I. Determination of 17-ketosteroids in the urine on the second hospital day showed a daily output of 15.9 milligrams dropping on the third day to 9.4 milligrams. These values are definitely elevated for a child of this age. The patient, after final grafting, was discharged on the one-hundred sixteenth hospital day.

S.M., (G.H.), a 4 year old female, was admitted to the hospital approximately 1 hour after having been severely burned. It was estimated that 46 per cent of the total body area was involved with second and third degree burns. Oxygen was given by nasal catheter. Local therapy included irrigation of the involved areas with saline, and gauze strips impregnated with 3 per cent aureomycin ointment were applied with pressure dressings. Adequate doses of procaine penicillin were administered as well as 3,000 units of tetanus antitoxin. Intravenous therapy consisted of 150 cubic centimeters of dextrose in Ringer's solution, 600 cubic centimeters of plasma, and 500 cubic centimeters of isotonic saline administered during the first 12 hours of hospitalization. A Foley catheter was inserted for adequate fluid output studies. Some of the blood chemistry studies for the first 10 days of the hospital stay are recorded in Table I. Determination of 17-ketosteroids in the urine on the second hospital day showed a daily output of 8.9 milligrams and on the third day 9.0 milligrams. These values are definitely elevated for a child of this age. On the twenty-sixth hospital day, under vinethine, ether anesthesia the patient was subjected to a second attempt at skin grafting. It was noted at this time that the first grafts had not taken. The patient was returned from the operating room cyanotic, in coma, and peripheral vascular collapse. Despite oxygen therapy she expired. The autopsy revealed cerebral edema, cloudy swelling of the kidneys, patchy atelectasis of both lungs, mesentery lymphadenitis, and a minimal bilateral hydrothorax.

A.E., (S.M.H.), a 7 months old male, was admitted to the hospital shortly after he was burned. The total extension of the burns was estimated to be 25 per cent, practically all third degree. Very little blood chemistry was done on this child since it was practically impossible to obtain blood samples. After admission, and before hypertonic sodium chloride was administered, 335 cubic centimeters of dextrose in water, 300 cubic centimeters of plasma, and 110 cubic centimeters of normal saline were infused. At the time this paper was written, the patient was still in the hospital after 137 days, practically completely grafted.

In order that the return of a sodium load in these burned patients could be compared with

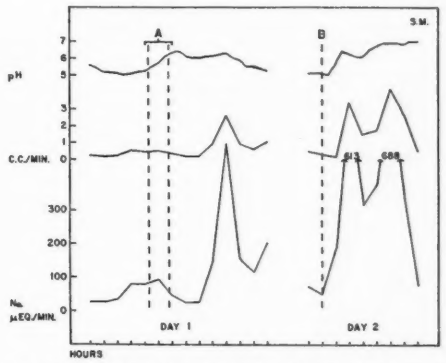

Fig. 3. The effect of the infusion of hypertonic sodium chloride on urinary *p*H, water diuresis, and sodium excretion in a severely burned child (S.M.). The infusions were given on 2 successive days at the times indicated by the dotted lines.

that of a normal person, intravenous infusion of 500 cubic centimeters of a 5 per cent sodium chloride solution was given a 57 year old man (F.R.) who was normal as far as kidney function and electrolyte balance were concerned. The percentage return following this sodium load was calculated (Figs. 2, 4, and 6). Urinary *p*H recording was carried out continuously for 2 days, and the urine was analyzed for sodium, potassium, ammonia, titratable acidity, and chloride. He exhibited pronounced urinary *p*H fluctuations and a normal excretion of electrolytes.

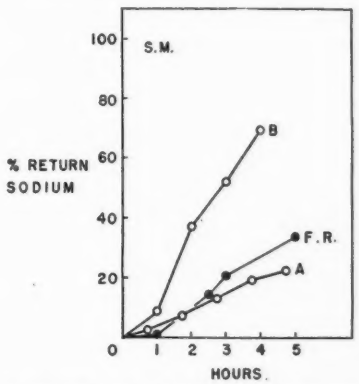

Fig. 4. The per cent of a sodium load recovered in the urine plotted against elapsed time is shown for a normal subject (*F.R.*) and a severely burned child (*S.M.*) (curves *A* and *B*).

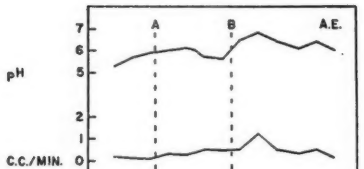

Fig. 5. The effect of the infusion of hypertonic sodium chloride on urinary *p*H, water diuresis, and sodium excretion in a severely burned child (A.E.). The infusions were given on 2 successive days at the times indicated by the dotted lines.

RESULTS

In Figure 1 is shown the effects of 3 infusions of hypertonic sodium chloride which were given the 8 year old boy, J.D., on the first, second, and third day following the burn.

Sodium chloride (300 c.c. of a 3 per cent solution) was given during a period of 1 hour (Fig. 1*A*). Urinary *p*H fluctuation was maintained but no increase in urinary output or sodium excretion resulted.

A second sodium load of 200 cubic centimeters of a 3 per cent sodium chloride solution was given the following day (Fig. 1*B*). This infusion was given for a period of 70 minutes and caused a considerable increase in sodium excretion as well as an increase in urinary output. The *p*H fluctuations were still present.

A third infusion of 200 cubic centimeters of 3 per cent sodium chloride which was given during a period of 40 minutes on the third day (Fig. 1*C*) resulted in an increase in urinary sodium excretion, output, and continuation of urinary *p*H fluctuations.

The percentage returns of these three sodium loads as well as the return of a sodium load to a normal person, *F.R.*, are depicted in Figure 2. It can readily be seen that the second and third loads (*B* and *C*) resulted in a much higher return in a shorter period of time, than that of the first load (*A*). This is a return (*B* and *C*) which is even appreciably higher than that obtained in a normal person (*F.R.*).

The 4½ year old girl, S.M. (Fig. 3*A*), received 170 cubic centimeters of a 3 per cent sodium chloride solution over a period of 1 hour and 40 minutes on the first day following her burn. The infusion was interrupted within this period for approximately 1 hour since the vein thrombosed and another cutdown had to be started. Therefore, the infusion is, in Figure 3, represented by 2 lines (*A*) indicating the start of each part of this infusion. Some hours later, an increase in the sodium excretion as well as the urinary output was noted.

The following day the patient received 150 cubic centimeters of a 5 per cent sodium chloride solution during a period of 20 minutes (Fig. 3*B*). It will be noted that there is an immediate increase in sodium excretion in the urine as well as urinary output and urinary *p*H. It will also be noted that following this there is a second peak of a high sodium excretion as well as a high diuresis. The reason for this is probably that immediately prior to it the patient received a rapid infusion of 400 cubic centimeters of a mixed isotonic electrolyte solution which ran in during a period of 1 hour. This went on unnoticed because the drop chamber had filled up so the rate of infusion could not be observed. It was discovered merely because the diuresis increased so greatly that the urine collection bottle filled up rapidly, and the urine ran out on the floor. Consequently, some was lost and the excretion per minute during that period is recorded lower than the actual figure.

The percentage return of these two loads as well as the return of the sodium load given the normal person, F.R., is seen in Figure 4*A* and *B*. As with the first patient the return of the first load (*A*) was poor, but the second (*B*) a good deal above normal (*F.R.*).

The 7 month old baby, A.E. (Fig. 5), approximately 18 hours following the burn, received 50 cubic centimeters of a 5 per cent sodium chloride solution (*A*) resulting in a slight increase in the sodium excretion, a slight increase in the output, and a slight increase in urinary *p*H. Approximately 5 hours later, 30 cubic centimeters of a 5 per cent solution of sodium chloride was given (*B*) which resulted in an immediate increase in urinary sodium excretion, urinary *p*H, and fluid output.

In Figure 6 is shown the percentage return of the two loads compared with the return in the normal person F.R. Again we find a low return from the first load (*A*) and one above normal resulting from the second load (*B*).

By comparing the total intake of sodium and the total urinary excretion of sodium, it was found in all 3 cases that a negative sodium balance was present at the third to fourth day following the burn. No signs of peripheral edema could be detected. The serum sodium, potassium, chloride, carbon dioxide as well as nonprotein nitrogen or blood urea nitrogen from the first 2 patients were relatively constant and normal for the first 10 days.

It might be feared that the administration of hypertonic sodium chloride would cause, as obviously was the case, an elevation of serum chloride and a depression of carbon dioxide. However, this condition was very temporary and did not give rise to any complications.

Following the parenteral sodium load, the patients were sustained on between 1 and 3 grams of sodium chloride per day given orally and a similar amount of potassium chloride. Thus a sodium excretion was maintained to keep balance and fluctuation in urinary *p*H.

The return of 500 cubic centimeters of a 5 per cent sodium chloride solution given intravenously to a normal adult person is presented in Figures 2, 4, and 6 (*F.R.*). The serum sodium was initially 144 milliequivalents per liter and the following hourly samples showed serum sodium of 147, 148, 147, and 147 milliequivalents per liter. In the normal person, the administration of the hypertonic solution caused an immediate rise in urinary *p*H which fluctuated markedly in the following 24 hours. The sodium return is comparable to the ones described by Crawford and Ludemann. They reported that both isotonic and hypertonic saline solutions are retained in the body for long periods, only 25 per cent at best being excreted within 3½ hours. They also mention that the recovery of administered electrolyte and water is not appreciably modified by previously loading the body with salt.

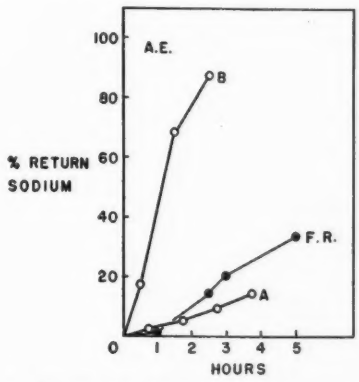

Fig. 6. The per cent of a sodium load recovered in the urine plotted against elapsed time is shown for a normal subject (*F.R.*) and a severely burned child (*A.E.*) (curves *A* and *B*).

DISCUSSION

The presented data indicate that the sodium retention seen following severe stress need not necessarily be a result of an increased adrenal activity. On the contrary, the increased adrenal activity seems to render the organism more capable of handling a sodium load provided that a sufficient initial amount of sodium in excess of the concentration in the serum has been given under such conditions. It is clearly seen in the 3 cases presented that the return of the sodium load is much greater than in a normal person. This may, in other words, be comparable with the way a Cushing patient will handle a sodium load. Whether the initial administration of a hypertonic sodium solution prevents a drop in serum sodium or restores an already lowered level is hard to evaluate from the available data.

If intravenously administered sodium in isotonic or hypotonic solutions is given a patient following a severe stress before a sufficient amount of hypertonic sodium solution has been given, it will apparently only serve to expand the extracellular volume and not give rise to any increased excretion of sodium in the urine. However, administration of even hypotonic solutions after an initial, sufficient load of a hypertonic sodium solution has been given seems to render the patient more capable of handling sodium than even a normal person. This seems very clearly to have been the case with patient S.M. who on the second day showed a high excretion of sodium in the urine immediately following a rapid infusion

of a solution which was hypotonic in respect to sodium.

We have had the opportunity of following 2 severely burned patients who did not receive an initial load of hypertonic sodium solutions. In both of these patients, the urinary *p*H remained fixed for a long period of time and this was concomitant with an almost complete lack of sodium excretion in the urine. Clinically these 2 patients exhibited extensive peripheral edema.

Although it is in no way possible to generalize from these few cases, it seems well worth while to emphasize that salt retention need not necessarily follow a severe stress, despite an increase in the adrenal activity, and that the maintenance of fluctuations in urinary *p*H seems to be useful as a guide to the amount and type of sodium which it is necessary to administer. It might finally be added that unless potassium therapy is started as soon as the diuresis is adequate, preferably on the first or second day, a serious condition of hypopotassemia may develop on the third or fourth day. It will be noted from Table I that no serious drop in serum potassium was seen in these 2 cases since oral addition of potassium chloride was already started on the first day.

SUMMARY

Three severely burned children were given an initial sodium load in the form of hypertonic sodium chloride in amounts which were sufficient to maintain fluctuation of urinary *p*H. Subsequent loads with hypertonic and hypotonic sodium solutions resulted in a return which was considerably higher than that of a normal person. It is concluded that increased adrenal activity need not cause sodium retention provided that the initial loss of sodium into cells or extracellular solids is made up for by the administration of a solution containing sodium in excess of the concentration in the serum. It is suggested to use the presence or absence of fluctuation in urinary *p*H as a guide to determine whether sufficient amounts of sodium have been given to prevent the posttraumatic complications of sodium and water retention.

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OSTEOID OSTEOMA

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N 1935 Jaffe described under the title of "Osteoid Osteoma" a distinct entity of lesions. These were benign osteoblastic tumors composed of osteoid tissue and ical bone. Instances of osteoid osteoma been reported under other names before 's original contribution, but the lesion not been recognized as a distinct clinicologic entity.

robably the first description of any consence was in 1926 by J. Heine. The lesion in the base of the proximal phalanx of the finger, and the pathologic evidence preted was not very convincing that the proc was on an infective basis. Hitzrot, in 1929, sented a case in the carpal scaphoid in ch the roentgen picture resembled Jaffe's inal description. In 1930 Bergstrand reted 2 cases, one in a metatarsal and the er in a phalanx of a finger. Both were clinlly diagnosed as osteogenic sarcoma; a retion of the metatarsal was done and an amtation of the finger was performed. In 1934 Milch described 3 cases very similar to Bergstrand and concluded that the entity was probably a benign osteoblastic tumor, forming osteoid tissue, and recommended surgical excision.

To Jaffe, however, must be given the credit for establishing the lesion as a distinct pathologic and clinical entity requiring local surgical excision. Since Jaffe's original paper, the literature has been flooded with reports of single and groups of cases. The total number of reported cases exceeds well over 200. Jaffe's cases alone are reported to exceed 100.

To review the pathologic and clinical characteristics of an osteoid osteoma, it may be stated that:

1. It is a small round or oval tumor-like nidus consisting principally of osteoid tissue and newly formed bone trabeculae placed in osteogenic connective tissue. It is never more than a centimeter in diameter. It develops in the spongiosa and in relation to the cortex of the affected bone.

2. There is usually, not always, an intense and dense osteosclerosis around this small nidus, so intense in radio-opacity that it may often completely mask the area of the translucency in the bone. Laminograms often are required for the specific diagnosis. The only lesion which produces a comparable osteosclerosis is an intracranial meningioma.

3. It has been found in all the bones of the body with the exception of the mandible and skull. It occurs most frequently in the shaft of long bones, especially in the bones of the lower extremity, and in undue proportion in the tibia. This makes one consider the possibility of trauma as an etiologic factor.

4. Pain is the outstanding symptom. It is persistent, progressive in intensity, worse at night, and usually is controlled or relieved by salicylates. The pain might precede the roentgen appearance in the involved bone by months.

5. The usual age incidence is adolescence.

Fig. 1. Anteroposterior and lateral views of right tibia of 19 months old child showing dense osteosclerosis suggestive of osteoid osteoma.

From the New York Orthopedic Hospital, Columbia-Presbyterian Medical Center, New York.

Fig. 2. Fig. 3. Fig. 4.

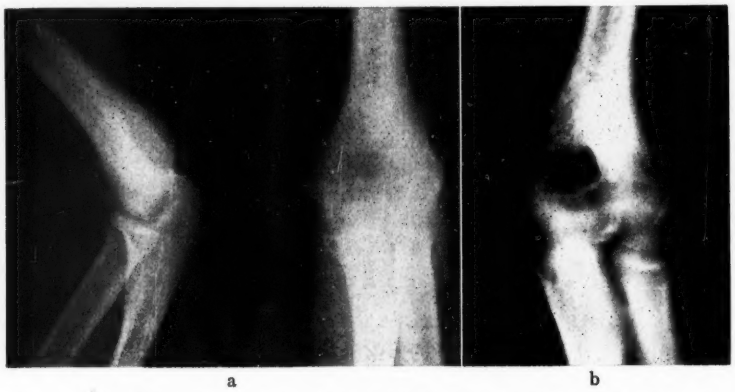
Fig. 2. Anteroposterior view of left femur showing subcortical nidus surrounded by area of osteosclerosis.

Fig. 3. Anteroposterior view of humerus showing subperiosteal nidus with very little osteosclerosis.

Fig. 4. Anteroposterior view of pelvis showing a large nidus in the ilium situated 1 inch above the acetabular margin.

MATERIAL FOR STUDY

Cases clinically diagnosed as osteoid osteoma at the New York Orthopedic Hospital were utilized in the study. The total number of cases was 32. Of these, in 21 the diagnosis was pathologically confirmed. In 8 the diagnosis was not established pathologically, but in view of the overwhelming evidence of clinical signs, roentgen appearance, and relief of symptoms with adequate surgery which involved removal of the area which contained the suspected nidus, no other diagnosis was



a b

Fig. 5. a, Anteroposterior and lateral views of right elbow showing osteosclerosis, periosteal proliferation with a questionable nidus in the olecranon fossa. b, Laminogram demonstrating position of the nidus in the lateral wall of the olecranon fossa.

Fig. 6. Anteroposterior and lateral views of left leg showing thickening of fibula. A clinical possibility of Ewing's tumor of fibula was also entertained.

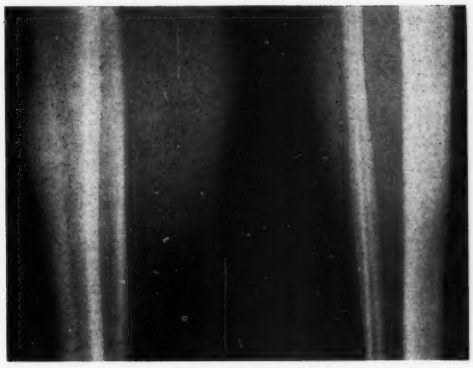


Fig. 7. Anteroposterior and lateral views of right leg showing thickening of fibula with a distinct lesion of the tibia.

table. In 3 cases the pathologist thought that the histologic picture was allied to, but distinct from, the pathologic picture of osteoid osteoma.

The average age incidence was 11.8 years. The youngest patient in our series was 19 months (Fig. 1) and the oldest 33 years. The youngest patient reported in literature was 14 months old and the oldest 55 years of age. The age incidence in our series was as follows: 3 patients between 0 and 5 years old; 5 between 6 and 10; 7 between 11 and 15; 8 between 16 and 20; 3 between 21 and 25; 2 between 26 and 30; and 4 between 30 and 35.

There were 27 males and 5 females.

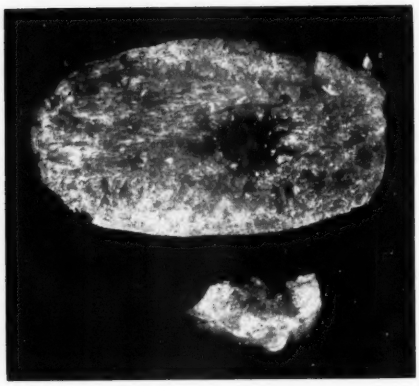
The following were the bones involved: tibia in 15 cases, ilium in 3 cases, femur in 6 cases, humerus in 3 cases, metacarpal in 2 cases, metatarsal in 1 case, fibula in 1, and phalanx (toe) in 1. Every bone in the appendicular and axial skeleton has been reported to be involved, including the ribs. Generally speaking, the lesion has a predilection for the bones of the lower extremity. In more than half of the cases the lesion was in the tibia and femur. It is less frequent in the upper limbs. Mary Sherman reported as high as 25 per cent incidence of osteoid osteoma of vertebrae in her series of 32 cases.

SYMPTOMS AND PHYSICAL FINDINGS

The predominant symptom was pain which was boring in character, usually at the site of the lesion. This was present in 30 of our cases. In 7 the pain was referred to neighboring joints. In all cases it gradually increased in severity. The pain was worse at night in 12. Nine patients had symptomatic relief of the pain with salicylates. In 2, painful limp was the principal complaint.

The constant physical finding was a swelling of the involved bone, usually with a point of exquisite tenderness, which corresponded to

Fig. 8. Anteroposterior view of femur demonstrating an intra-articular lesion in the neck of the femur with two distinct calcific spots.



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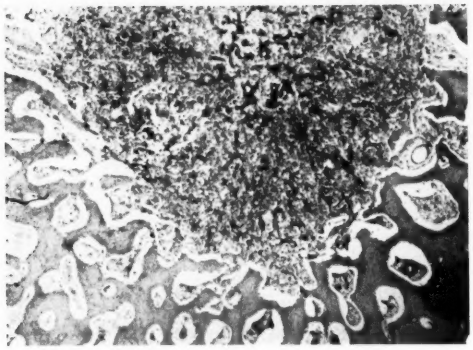

b

Fig. 9. a, Gross appearance of specimen of femur removed showing the nidus. b, Characteristic microscopic appearance under low power (×50) of the nidus.

the nidus, in the bone. This was especially true in the tibia. In the case of the femur and the acetabulum the patient had diffuse pain, and no point of acute tenderness could be elicited. In 1 case, in which there was an intra-articular lesion of the neck of the femur, there was marked spasm of the muscles about the hip. Another, with a lesion of the lesser trochanter, had a flexion contracture of 10 degrees. Local redness with limitation of joint motion and heat was present in a patient who had an intra-articular lesion of the elbow, which was clinically diagnosed as tuberculosis of the elbow. In none was there a systemic reaction. Only 1 patient had lost weight and he complained of loss of appetite as well.

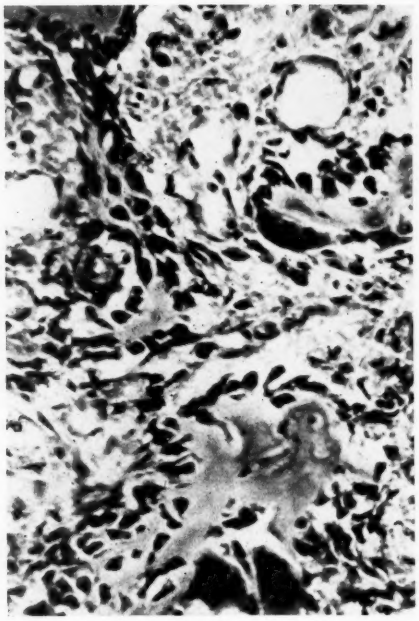

Fig. 10. High power appearance (×500) of the nidus showing plasma cells, macrophages, and giant cells interspersed with osteoid tissue.

Fourteen of the 32 gave a history of trauma to the part involved, but in only 3 cases did the trauma precede the onset of pain.

LABORATORY DATA

Routine blood tests and urinary studies were of no value. Only 1 patient had an elevated sedimentation rate. In cases in which the diagnosis was in doubt and a battery of tests was performed, the results were all inconsequential.

ROENTGENOLOGIC DATA

A typical roentgen picture is almost always present in all cases if proper time has elapsed between the onset of pain and the appearance of the nidus. The classic picture is a dense osteosclerosis with usually a centrally placed translucent zone that may vary from 2 or 3 to 15 millimeters in cross section, as demonstrated in the roentgenograms of the femur and humerus (Figs. 2 and 3). The size of the nidus may, however, be larger than the size

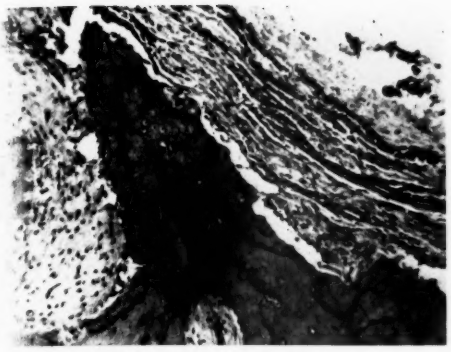

Fig. 11. Low power appearance (×100) of periosteum showing proliferation and lymphocytic infiltration.

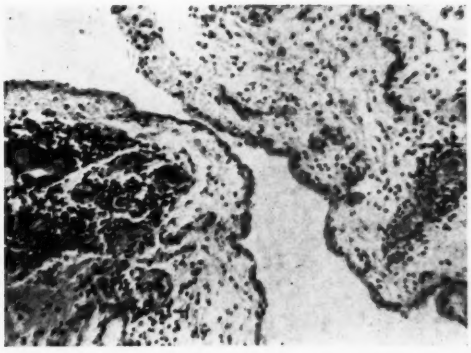

Fig. 12. Low power appearance of synovia showing edema, hyperemia, and lymphocytic infiltration.

mentioned as the lesion in the ilium demonstrates (Fig. 4). The nidus might be missed in the regular roentgenograms because of the dense osteosclerosis surrounding it and laminograms are an occasional necessity for the establishment of the diagnosis preoperatively (Fig. 5a). This is well demonstrated in the laminograms of the lower end of the humerus (Fig. 5b). The periosteal proliferation may be so marked that in 1 case a diagnosis of Ewing's sarcoma was made roentgenologically (Fig. 6). There is also sometimes a reactive proliferation of the neighboring bone with thickening of the fibula with a distinct lesion in the tibia (Fig. 7). Osteosclerosis may sometimes be completely absent and this is a noticeable feature in the ilium. Irregular foci of calcification in the center of the nidus are common findings. We do not have a case with 2 distinct lesions in the same bone or in the same individual. In 1 case of an intra-articular lesion in the neck of the femur there were 2 distinct calcific spots corresponding to the 2 distinct areas of calcification of the nidus (Fig. 8). The nidus may be cortical (Fig. 2), intramedullary, or subperiosteal (Fig. 3).

PATHOLOGIC FEATURES

Grossly the specimens of osteoid osteoma exhibited no particular characteristic. There was always dense sclerotic bone except in 2 instances, one in the ilium and the other in the terminal phalanx. The cortical osteosclerosis varied with each individual case, but did not have any direct relation to the duration of the complaint. Invariably, they contained an area of pinkish or red granulation tissue, which was the nidus (Fig. 9a). The focus was never very large, the average size being between 7 and 8 millimeters. Sometimes it was less than 3 millimeters. Therefore, it is extremely easy to miss the nidus especially when curretting. Hence, when in doubt, it is advisable to take an x-ray film on the operating table to be sure that the nidus has been removed. The small size of the lesion is also at times responsible for missing the nidus, as probably has occurred in 8 of our cases.

Microscopically, there are usually a large number of mesenchymal cells scattered irregularly in the field with abundant osteoid tissue appearing as a pale pink substance (Fig. 9b). However, there are certain features which place the neoplastic origin of this lesion in considerable doubt. Principally, these are:

1. Plasma cells were especially noted in fair number in 3 cases. However, in 10 no inflammatory cells were noticed at all (Fig. 10).

2. Lymphocytic infiltration of the periosteum was noticed in 2 cases, very markedly in 1 with edema of the layers and inflammatory cell infiltration (Fig. 11).

3. Foreign body giant cell reaction and hemorrhage with phagocytosed hemosiderin were seen as a constant feature (Fig. 10).

4. In 1 case, in which the muscle had been biopsied to be sure there was no evidence of invasion by tumor tissue (in which the clin-

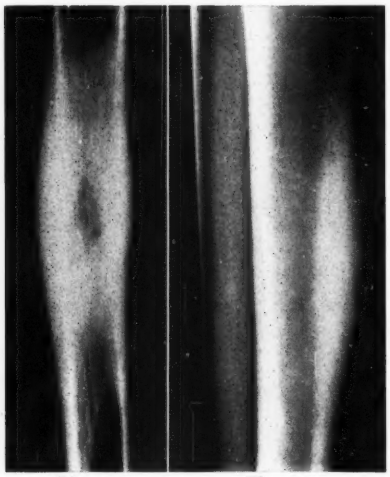

Fig. 13. Fig. 14.

Fig. 13. Anteroposterior view of right femur showing Brodie's abscess.

Fig. 14. Lateral of left tibia showing congenital luetic osteitis simulating osteoid osteoma. Case was proved by biopsy.

ical diagnosis of Ewing's tumor was made), the muscle showed definite evidence of lymphocytic infiltration suggesting a myositis.

5. In 1 case in which the synovia was involved by an intra-articular lesion, the synovial membrane showed extensive edema, moderate hyperemia, extensive focal infiltration by lymphocytes and plasma cells, and infrequently some polymorphonuclear leucocytes (Fig. 12).

Calcification of the nidus was not an uncommon finding.

Bacteriologically, no positive culture was obtained in any of the 32 cases.

DIFFERENTIAL DIAGNOSIS

The most important conditions which could be mistaken for osteoid osteoma are Garre's sclerosing osteomyelitis, Brodie's abscess (Fig. 13), syphilitic osteitis (Fig. 14), and tuberculous osteomyelitis. In the last two conditions there are specific diagnostic aids. Fibrous dysplasia and eosinophilic granuloma may also be mistaken.

TREATMENT

Excision of the lesion is the only satisfactory cure which results in complete remission of the symptoms. It is advisable when practicable, to do the same under a tourniquet and remove the nidus with a portion of the involved sclerotic bone, not all of it, since weakening of the shaft may result if too much bone is removed. For this purpose, it is advisable to obtain roentgenograms at the time of surgery.

COMPLICATIONS

One patient suffered a pathologic fracture after excision of too much of the thickened cortex. One patient had intransigent ankle edema as a result of thickened adherent scar on the medial side of the tibia.

CONCLUSION

Thirty-two cases of osteoid osteoma have been reviewed and their salient clinical, roentgenologic, and pathologic features discussed. A few points in the satisfactory management of the condition are suggested.

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ADENOSIS OF THE FEMALE BREAST

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ADENOSIS is defined as unencapsulated parenchymatous hyperplasia. The foci may be single or multiple, but are practically always bilateral. The disorder is a very common one. Different forms of adenosis have been described sporadically in the literature, and an excellent account has been given by Geschickter in his chapter on mastodynia. Nevertheless, little has been done in the way of exact anatomic classification, and although the general opinion is that these lesions are not precancerous, information is needed on their ultimate outcome. With the advent of x-ray diagnosis a more accurate follow up can be achieved than was hitherto possible.

Parenchymatous hyperplasia in one form or another accompanies dysplasia in the majority of patients under 50 years of age. However, in an unselected series of 618 breast operations performed at the Albert Einstein Medical Center adenosis occurred alone in 50 cases and was the reason for the patient's hospitalization. This is a fairly large group and with the present day tendency to operate on every lump in the breast, no matter how insignificant, the number is steadily increasing. It behooves us, therefore, to take stock and try to evaluate the nature and importance of these lesions.

CLINICAL FINDINGS

The youngest patient in our series was 21, the oldest 49 years of age, i.e. the lesions occurred during the period of sexual activity. The age groups corresponded closely to those given by Geschickter. In all, ovarian function was intact. As is usual in dysplasias, a considerable proportion (20 in all) had pelvic or thyroid disorders. Six patients had received hormone medication before the mass appeared, 3 had allergies of one type or another. "Nervousness" was very common. A family history of breast disorders occurred 8 times in mothers or sisters, but only 1 patient, the monovular twin whose history is given later, told of carcinoma of the breast in the next of kin. Family histories of carcinoma, other than breast or uterus, were given by 4 patients. In 3, the tumors were in more than 1 member of the family.

The symptomatology of adenosis is variable and often distinctive. Common to all cases in some degree is the presence of a mass or multiple masses and these are usually associated with premenstrual pain. Duration is extremely variable, ranging from 2 days to 8 years in our patients. Variations in the size and sometimes in the location of the swelling are characteristic, especially in early cases. Twenty-three patients in our series gave this history. In most cases the increase was premenstrual (14 patients) and was followed by regression after the period, but 1 had intermenstrual swelling and in 1 the mass diminished following administration of testosterone. In 1 patient the mass recurred after removal. Nine of this group had premenstrual tumors up to several centimeters in diameter, sometimes with reddening of the overlying skin; in the postmenstrual phase the tumors vanished. The most that could be palpated was a slight thickening of the affected area. In 13 women the mass had not been present long enough for alteration in size to be noted. Fourteen patients had not detected changes in size although in those with premenstrual pain some alteration was probably present. Since all the cases reported came to operation it is not possible to state whether any of the tumors would have regressed permanently. However, many patients give a history of a lump which disappeared months or years before, and our present experience inclines us to believe that most of these were foci of adenosis.

On clinical examination the masses closely resembled cysts or fibroadenomas, so much so that in stationary tumors in which the history did not give a clue, diagnosis could only be made by x-ray examination. On several occa-

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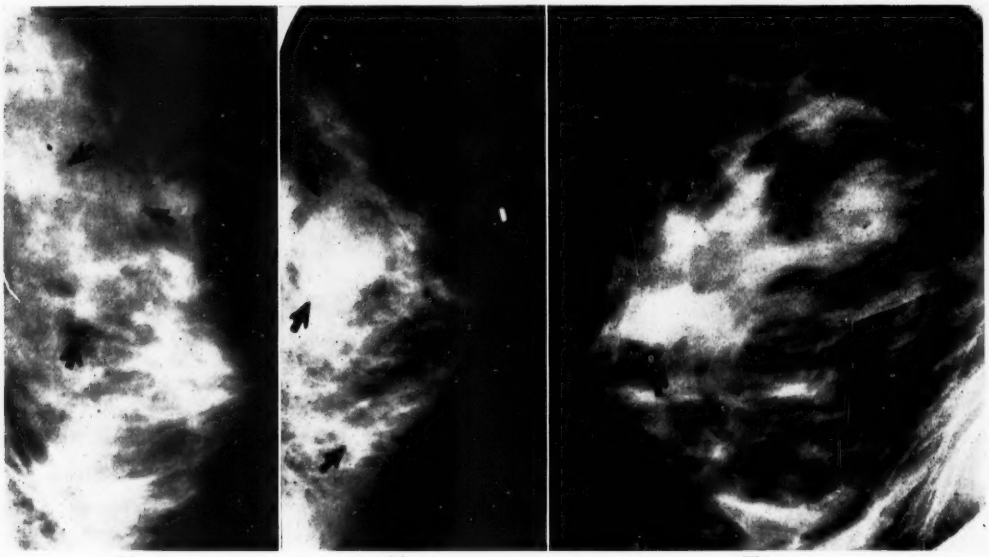


Fig. 1. Fig. 2. Fig. 3.

Fig. 1. Adenosis types A and B; moderate fibrosis. Case 407, age 40 years. Painless mass in left upper quadrant noted 1 week. The x-ray film shows a poorly defined mass in the left upper outer quadrant. Where definite margins are visible they are smooth and discontinuous. Other small opacities are scattered through the remainder of the breast. The right breast was similarly involved.

Fig. 2. Adenosis. Case 424, age 40 years. Premenstrual swelling and soreness of breasts for 2 months. One month previously a mass was found above the nipple. This became harder before the menses. On examination 16 days after the period a movable mass 3 centimeters in diameter was palpated in the left breast above the nipple area. Smaller masses were felt nearby and in the opposite breast. The x-ray film shows an irregular opacity in the upper part of the breast surrounded by similar smaller areas. Where definite margins are seen they are smooth and discontinuous. A second smaller opacity appears in lower part of breast.

Fig. 3. Adenosis. Case 433, age 32 years. Mass in left breast 2 months, first noted before a period. It increased in size before the last period. On examination a nodular mass extended through most of the left breast. A similar smaller mass could be felt in the right breast. The clinical diagnosis was multiple cysts and certainly by palpation no other conclusion could have been reached. But repeated roentgenograms failed to reveal cysts. There were instead multiple irregular opacities of the ground glass type, separated by clear zones of fat. At operation 2 pieces of firm breast tissue were removed. They contained neither cysts nor tumor. Microscopically, there were areas of adenosis type B separated by dense connective tissue in which remains of involuted lobules could be made out.

sions we were astonished to find no cysts in the film and thought our technique must be faulty. At operation the x-ray reading was vindicated. The specimen showed more or less firm, sometimes slightly nodular breast tissue in which a few pink spots might be seen and occasionally a small pinkish patch. In some cases the gross could not be distinguished from normal breast.

ROENTGENOLOGY

On the x-ray film, adenosis appears as fluffy or blurred opacities with a texture suggestive of ground glass (Fig. 1). The patches are oval or partly oval rather than round. Breast trabeculae are visible through these opacities. The involved areas may be partly outlined by curvilinear margins (Fig. 2). These margins will then appear sharp like those of a fibroadenoma or cyst. However, closer inspection shows that portions of the margins are irregular. This semblance of incomplete capsulation appears as if the lesion had set out to be a fibroadenoma but had not completed the job; and this is precisely what is seen in many pathologic specimens. In older or obese women with fatty breasts, the "ground glass" opacities of adenosis are isolated between clear zones of fat (Fig. 3). In all our cases the films showed bilateral symmetric lesions, more developed on one side than the other. In generalized adenosis the films were dotted

Fig. 4.

Fig. 5.

Fig. 4. Generalized adenosis, with transition to mazoplasia II. Case 759, age 36 years. For the past 6 months the patient had complained of stinging in the breasts and premenstrual heaviness. Masses were found in both breasts by her physician. Clinically they resembled cysts. The x-ray film shows widely scattered irregular opacities throughout both breasts. At operation a few cysts 2 to 3 millimeters in diameter were seen. Microscopically there was adenosis type B with considerable basal and myoepithelial proliferation and rather marked fibrosis.

Fig. 5. Multiple cysts. Case 878, age 44 years. Mass in right breast noted 6 months, tender before periods. On examination multiple large and small cysts were felt in both breasts. The x-ray film shows multiple, round, sharply defined opacities. Since the cysts are superimposed on each other, many are not seen in their entirety. A number of them impinge on the subcutaneous fat. The superficial margins are then clearly seen. In the deeper part of the breast are some fluffy opacities corresponding to areas of adenosis also seen in the microscopic sections. At operation cysts of all sizes were found, of both mazoplastic and secretory type.

over with small fluffy opacities reminiscent of melting snowflakes (Fig. 4).

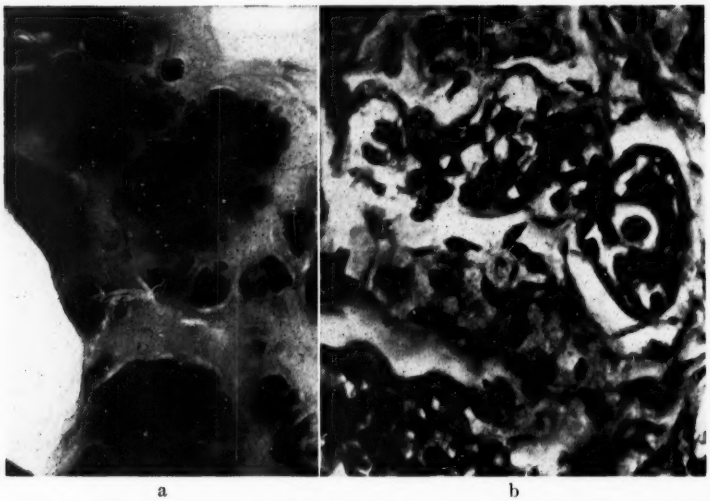
Adenosis must be distinguished on the film from cysts or fibroadenomas which at times it closely resembles. The following points should be borne in mind:

1. The lesions of adenosis are bilateral. The margins are indistinct, at any rate around part of the mass.

2. Cysts and fibroadenomas show smooth sharp margins not connected with breast trabeculae (Fig. 5). As we have noted previously (5, 6), breast trabeculae run over them but are not present within the lesion. If the presence of a cyst or fibroadenoma is suspected, every effort should be made to delineate it on the film. If the technique is satisfactory, failure to show the mass should lead to a reconsideration of the diagnosis in favor of adenosis. A large area of adenosis may obscure a fibroadenoma or a cyst. A blue domed cyst may occupy the center of an area of adenosis and thus be rendered invisible. In such a case, it is the adenosis, not the cyst, which is important.

PATHOLOGY

The pathology of adenosis is best explained by reference to the normal menstrual cycle. The menstrual cycle in the mammary gland has been the subject of much discussion. Confusion has arisen owing to the variability in the amount of parenchyma, the number, size, and distribution of lobules and the degree of



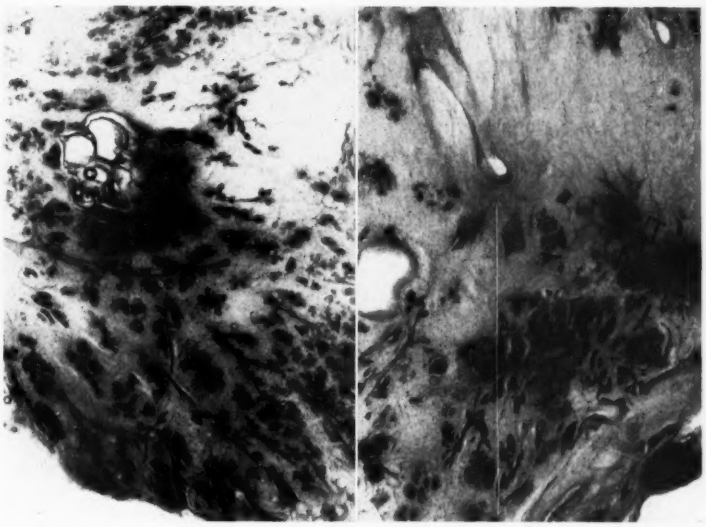
a b

Fig. 6. a, Adenosis type A. Slicer section, × 3.5. Case 331, age 44 years. Indefinite mass in right breast noted 7 days. Hysterectomy 3 years before, ovaries not removed. The x-ray film showed an opacity which resembled a fibroadenoma except that the edges were not smooth. The illustration shows some very large lobules which are for the most part normally developed. b, Adenosis type A. Paraffin section, × 257. Case 772, age 23 years. To show postmenstrual degeneration of ductules. In the duct near the center the epithelium has disappeared and only a few myoepithelial cells are still recognizable.

cyclic growth and regression in different women and in different parts of the same breast. Moreover, only some lobules undergo changes during a given cycle and they may not do so simultaneously. Bearing all this in mind, the following description may be taken as the physiologic norm. It is based on the author's (H.I.) observations from 1929 onwards, supplemented by the work of Grynfeltt and Dabelow.

In the postmenstrual phase there is budding out of ductules to form new lobules. The first stage is a proliferation of cells at some point in the wall of a duct, probably a prelobular duct although growth from larger ducts is also noted. Soon a lumen appears, the duct grows, and ductules arise from it. Growth and branching continue until a lobule is formed. The epithelial cells at this stage stain deeply, due to dense nuclear chromatin. As the cycle progresses, both epithelial and basal cells become larger and paler. Meanwhile some of the basal cells show blunt processes. These elongate, become striated, and myoepithelial cells are formed. A few days before the period a little protein material is secreted into the ducts. The epithelial and basal cells become vacuolated. During menstruation the basal cells break up and the epithelium is shed into the lumen. In the premenstruum the prelobular and intralobular ducts dilate. Imbibition of fluid as well as secretion contributes to the dilatation. The intraductal tissue is dense and fibrous in the postmenstrual phase and fills the gaps left by degenerated ductules. In the premenstrual phase it is loose and edematous and has scattered mononuclear cells.

Owing to the variability of the normal breast it is easy for the surgeon to mistake a group of developing lobules for a tumor and remove them. Microscopically it may be impossible to draw a line between the earliest phase of adenosis and normal lobules. Apart from these doubtful lesions one may, in theory at least, classify adenosis into four types of lobular dysplasia. More than one type may be present, but usually one is predominant and evaluation is made accordingly.

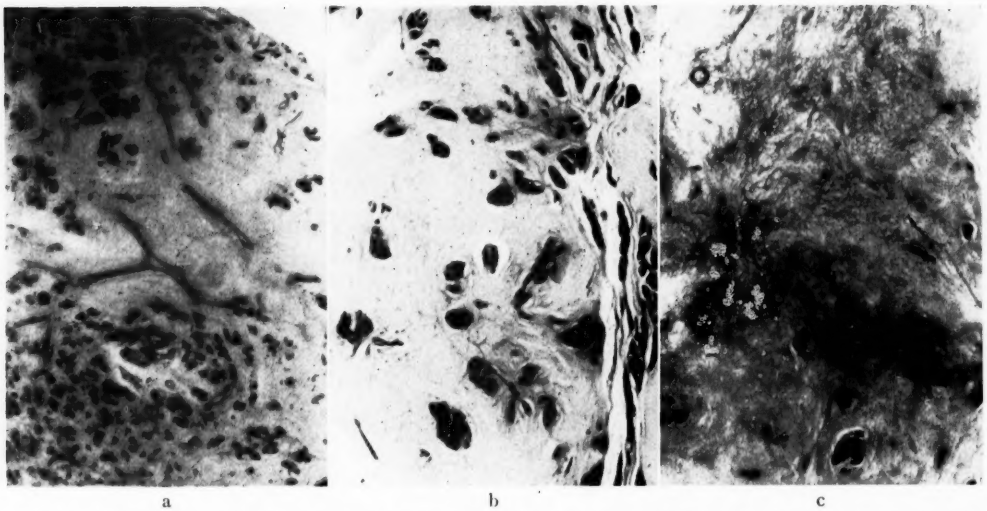


a b

Fig. 7. a, Adenosis type B. Slicer section, × 1.3. Case 543, age 33 years. Illustration shows a large number of poorly developed lobules consisting of relatively few dilated ductules. Some lobules are represented by clusters of small cysts. A group of slightly larger cysts is seen in one place. This case showed very early transition to mazoplasia II with simple cysts. b, Adenosis type D (sclerosing adenosis). Case 173, age 49 years. Slicer section, × 1.3. The section is from a case of mastopathy in which there were many areas of adenosis. The illustration shows some tangled, partly fibrous structures intermingled with fine fibrils (adenosis type D). Cysts are also present.

Type A consists of lobular hyperplasia with normal development of ductules. Sections show very large lobules or numbers of smaller lobules lying close together (Fig. 6). The ductules are lined by many more cells than usual. The epithelium tends to be pushed up in places by the multiplication of basal cells which are increased over those of the normal breast. Transition between these cells and myoepithelium is seen and as the cycle advances there may be a continuous sheet of myothelial cells lying on the basement membrane. Sheaves of these cells grow into the surrounding tissue. The myoepithelium is especially conspicuous around the prelobular and intralobular ducts. This is not surprising since these ducts act as reservoirs and the contraction of myothelial fibers is responsible for the ejection of milk during suckling. At the time of the menstrual period it is common to find only a few ducts undergoing involution (Fig. 6b), but in some cases the entire lobule degenerates.

Type B is the commonest form of adenosis. The lobules consist of a few more or less dilated ductules (Fig. 7a). In this type there is incomplete lobular development owing to failure to form dichotomous branches. At various stages of lobular development the walls of the ductules grow as a whole without reference to specific growing points. The result is wider and longer channels and eventually the formation of cysts. These lobules must be distinguished from the club-shaped ducts of the adolescent and from similar formations due to lack of lobular development in mazoplasia of Cheatle and Cutler. In this form of adenosis, involution is possible but less likely than in type A. Should the disorder progress, a transition to the condition we have described as mazoplasia II takes place. Mazoplasia II is characterized by smooth-lined cysts, either large or small, an increase in intraductal connective tissue, patches of adenosis, as well as a tendency to the formation of fibroadenomas.



a b c

Fig. 8. a, Recurrent tumors. Slicer section, × 1.2. Case 326, age 27 years. For the past 7 months the patient had a mass in the left upper outer quadrant which increased greatly in size at the time of the menses. Later it subsided and was often difficult to feel. Her last period began January 16. On January 21 the breast was found to be swollen. Two days later the area was red and tense and the mass was 3 to 4 centimeters in diameter. On January 30 the swelling had disappeared and all that could be felt was an indefinite thickening with one narrow, cord-like duct. The operation specimen presented firm, slightly nodular breast tissue, speckled with minute ducts. Paraffin section showed lobules consisting of a few dilated ductules. The prelobular ducts were a little dilated. There was epithelial and myothelial hyperplasia. The left breast had been operated on 2 years before for a similar condition. b, Slicer section, × 2.5. Case 138, age 28 years. Large, painful, recurrent mass in the left upper outer quadrant for 7 months. The tumor attained its greatest size 2 weeks after the menstrual period. It disappeared with the onset of the menses. When first seen it was felt as a large cystic mass. Six days postmenstrually no tumor could be palpated. Because of pain and the patient's fear of carcinoma, the upper outer quadrant of the breast was removed. Grossly the tissue was firm and a little nodular. Microscopically groups of irregularly developed lobules were separated by areas of fibrous tissue. The illustration shows some large compact lobules (adenosis type A), some with sparse, rather widely separated ductules (adenosis type B), and some which are undergoing involution. c, Fibrosis following adenosis. Slicer section, × 2.5. Case 552, age 38 years. Tender mass in the upper outer quadrant of the left breast gradually increasing in size for 10 months. On examination several cyst-like masses were felt in both breasts. The mass in the upper outer quadrant was removed. It consisted of fibrous tissue with occasional aggregations of lobules. There was no tumor. The fibrous pattern is characteristic of lobular involution not of mazoplasia I.

Type C, which is difficult to distinguish from the foregoing, is present near the tumor in most carcinomas of young women, and must, therefore, be regarded with grave suspicion. In these breasts the adenosis is widespread, but there are no large cysts. The lobules have the same general conformation as in type B. The essential distinction seems to be a disturbance in the organization of the walls of the ductules. Myothelial cells are scarce. Suspicion may be aroused by finding some ductules with epithelial and basal, but no myoid proliferation. Should proliferation of undifferentiated cells persist, epitheliosis (accumulation of cells within the duct) may well supervene. We agree with Dawson that epitheliosis is significant as a precursor to carcinoma.

Type D is the sclerosing adenosis of Urban and Adair (Fig. 7b). Often these formations consist entirely of myoepithelium and we believe that although the term adenosis is correct in that they are derived from epithelium, it would be less confusing and more concise to use the term myoid sclerosis. All stages of myoid development may be studied in these nodules, from the large embryonic type of cell similar to that of early pregnancy to complete fibrosis with disappearance of nuclei.

When adenomatous nodules undergo involution the epithelium degenerates as in the normal menstrual phase, the myoid nuclei be-

come attenuated and disappear and only the fibrils, which now take collagen, instead of muscle stains, are left. Besides conversion into fibrous tissue the myoid cells frequently undergo hydropic and mucoid degeneration.

The factors responsible for premenstrual swelling in adenosis are parenchymatous growth, imbibition of fluid, and vascular dilatation. In type A lobular growth is obvious. In type B the wide cystic ductules although fewer in number, take up more space. In both A and B the prelobular and intralobular ducts are unduly dilated. Disappearance of many of the lobules in the postmenstrual phase together with absorption of fluid accounts for postmenstrual shrinkage. Should postmenstrual involution be frequently repeated, the area of adenosis may be replaced by fibrous tissue (Fig. 8a, b, and c).

Fig. 9. Mazoplasia I. For comparison with Figure 8 c. Slicer section, × 2.2. Case 72, age 32 years. The fibrosis is clearly intraductal. The lumen of the ducts is small and has sometimes disappeared. The epithelium is atrophic.

DISCUSSION

The importance of adenosis does not lie with the lesion itself, but with its ultimate fate. Pathologic classification is of value only insofar as it allows prediction of the ultimate outcome. The object here is prognosis rather than diagnosis. Obviously, years of study and follow-up of patients will be required before our aim can be fully achieved, but we believe that a beginning can and should be made.

Foci of adenosis are more often multiple than single. Should one take the gloomy view that all of them could be precancerous the only sure remedy would be to remove both breasts, a procedure that even the most radical surgeon would hardly recommend. As a matter of fact type B, which comprises some three-fourths of the cases, is definitely not a precancerous lesion. Type A is probably the first stage of proliferation. It is often found with other types especially B. It could be the early stage of any of them, except C, in which there is lack of myoepithelial cells. Its significance should be judged by the company it keeps. There is no a priori reason why the hyperplastic lobules should not resolve completely. Failing this, a small focus is liable to develop into a fibroadenoma and the same may be said of type B. Type D, sclerosing adenosis, while difficult at times to distinguish from carcinoma, is a benign lesion. It is associated with types A and B and is common in mastopathy (Schimmelbush disease). It also takes part in the formation of fibroadenomas. Type C, which is deceptively like B on superficial examination, is dangerous and any patient exhibiting it must be kept under observation. Our attention was originally called to this type by the case of a young woman of 28 years, an identical twin. Her mother died of carcinoma of the breast. Her sister had developed carcinoma 4 months previously and has since died. In our patient a sudden swelling appeared 8 days before menstruation in the outer part of the left breast, the area corresponding to the sister's carcinoma. It was removed 10 days later. No pathology could be detected grossly, but microscopically the breast was typical of adenosis type C. The patient has been under observation now for 4 years and has remained well. Since 80 per cent of identical twins are liable to identical tumors, the operation may well have prevented the development of a carcinoma. It may be added that slicer sections showed the same type of breast parenchyma in both sisters. In another case in which histologically malignant cells were found in ducts (carcino-

ma in situ), myoepithelial cells were extremely difficult to find in the affected area. Both cases emphasize the need of caution in dealing with this type of adenosis.

The relationship of adenosis to mazoplasia as described by Cheatle is not clear. We would now diagnose adenosis rather than mazoplasia in the older age group. Mazoplasia I in our classification (4) is used to denote breasts of the fibrous type, also described by Cheatle, in which lobules are scanty or altogether absent. The entire breast in 2 such cases was cut serially. No lobules were found. The ducts ended in a cluster of club-shaped swellings like those of the adolescent. They differed from adolescent breasts in that there was an abnormal amount of intraductal fibrous tissue (Fig. 9). Areas of lobular proliferation are possible in such breasts but are not common. On the other hand, fibrosis is the final stage in many cases of adenosis. No final opinion can be given at this time, but it seems to us that mazoplasia in young women is not necessarily adenosis.

Recognition of the clinical groups that emerge from this study should be of value in the treatment of adenosis. The facts suggest that disappearing tumors in young women may be safely let alone. If a fibroadenoma supervenes it can be dealt with later. The same may be said of long-standing masses resembling cysts or fibroadenomas which do not alter in size. It is here that x-ray diagnosis is of value. If the history and physical findings point to a benign, possibly cystic lesion and no tumor is visible on a technically satisfactory film, it is safe to make a diagnosis of adenosis, probably with fibrous involution of most of the lobules. The only reason for intervention would be a strong family history of carcinoma of the breast. Multiple masses which wax and wane are mostly benign. But when nodules are very numerous and the histologic type of all of them cannot be known there is danger, albeit remote, of a carcinoma developing unnoticed most often after the menopause and perhaps when the adenosis masses are more or less stationary.

SUMMARY

Adenosis is a common condition of the breast which is frequently not diagnosed or is mistaken for other lesions. Except for pain and the disappearance of tumors, the symptomatology is not pathognomonic. In many doubtful cases the x-ray examination will lead to the diagnosis. The following x-ray criteria are based on a review of 618 breast operations which included 50 cases of uncomplicated adenosis: (1) discrete ground-glass opacities are seen with irregular outlines; (2) some lesions are partially outlined by sharp margins resembling incompletely encapsulated fibroadenomas; (3) lesions are bilateral and vary in size and shape; (4) cysts and fibroadenomas are distinguished from adenosis by their smooth sharp margins; (5) trabeculae merge with areas of adenosis, but are displaced by cysts and fibroadenomas.

Microscopically, four types of adenosis may be distinguished: type A, well formed lobules with hyperplasia of epithelial and myoepithelial cells; type B, lobules consisting of dilated ductules with hyperplasia of myoepithelium; type C resembles type B but with scanty or absent myoepithelium; type D, sclerosing adenosis.

Adenosis may disappear, undergo fibrosis or lead to cyst formation. One form (type C) may be precancerous.

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SURGICAL OCCLUSION OF THE ANTERIOR CHOROIDAL ARTERY IN PARKINSONISM

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THE lingering, imprisoned helplessness that has come to be recognized and resolutely accepted as the usual final stage of parkinsonism is well known. Moreover, the relative ineffectiveness of therapy in mitigating the disability of this disorder has been commonly acknowledged. As recently as 1951, in reviewing the results of all medical therapy used in parkinsonism, Schwab and Prichard stated that the improvement to be expected even with the best drugs is comparatively slight. In the same year, Ebin summarized a review of all known methods of surgical treatment of parkinsonism by stating that rigidity could not be consistently relieved by any of the surgical procedures used in parkinsonism and that relief of tremor could not be accomplished without *at least* moderate loss in motor power. Ebin further stated that in so far as surgery is concerned it appeared certain that "we have gone as far as we can go," and that it was improbable that rigidity or tremor could be relieved surgically without interference with motor function. This opinion, heretofore shared by many, appears in light of recent investigations to have been overly pessimistic. It is the purpose of this report to summarize our investigation to date of a new approach to the treatment of this disorder. This approach consists of surgical occlusion of the anterior choroidal artery (5, 6).

In October 1952, during a craniotomy originally planned as a pedunculotomy in a 39 year old man incapacitated by right-sided tremor and rigidity, the left anterior choroidal artery was torn and had to be completely occluded. Because of uncertainty as to the possible sequelae of occlusion of this vessel, the operation was terminated without cutting the peduncle. The postoperative course was notable for virtual disappearance of tremor and rigidity from the right extremities, without any lessening of motor power in these extremities.

During the postoperative observation of this patient, one could not suppress the speculation that the unplanned arterial occlusion had contributed to the alleviation of tremor and rigidity in this case. This speculation led to the present investigation.

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This study assisted by the Allen P. and Josephine Green Foundation.

THE ANTERIOR CHOROIDAL ARTERY

The anterior choroidal artery arises from the internal carotid artery at a varying level between the posterior communicating and middle cerebral arteries. It passes backward and medially along the optic tract and terminates over the lateral geniculate body. There are branches to the globus pallidus, ansa lenticularis, hippocampal formation of the temporal lobe, retrolenticular portion of the internal capsule, lateral geniculate body, and choroid plexus. There are rich vascular anastomoses with the posterior choroidal artery over the lateral geniculate body.

RATIONALE OF THIS OPERATION

Shellshear has demonstrated that arteries together with cerebral structures constitute functional units; neurovascular mechanisms of which neither component is independent of the other, and that the arteries of the brain are as much a part of the neurovascular mechanism as is the brain itself. Abbie (1, 2) in his classical study of the blood supply of the basal ganglia, concluded that the globus pallidus and its efferent connections through the ansa lenticularis with the corpus subthalamicum, ventrolateral nucleus of the thalamus, substantia nigra, and red nucleus constitute a single functional unit which is dependent for its blood supply upon the anterior choroidal artery. Thus it was hypothesized that occlusion of the anterior choroidal artery might

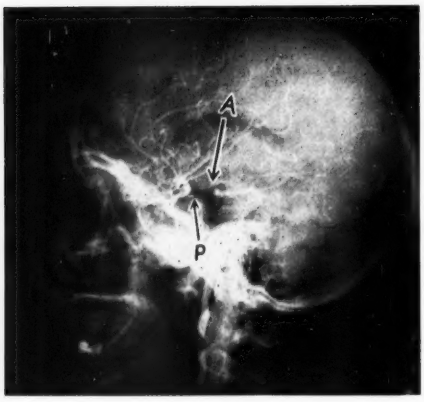

Fig. 1. Left carotid arteriogram demonstrating origin and course of anterior choroidal artery (*A*), and its relationship to the posterior communicating artery (*P*). Both vessels are seen to lie in the basilar cisterns, which in this case are demonstrated by contrast pneumocisternography.

affect the elements of this phylogenetically determined "functional unit" in a more selective manner than had previously been accomplished by other methods.

The question of collateral circulation was considered. However, it has been demonstrated that although this vessel has anastomoses over the surface of the lateral geniculate, the branches that enter the brain substance to supply the globus are end arteries without any collateral supply. Therefore, if the anterior choroidal artery is occluded both at its origin from the internal carotid and again more distally after the deep branch to the pallidum has emerged, the likelihood of collateral retrograde blood flow from the posterior choroidals reaching the latter structure can be obviated. Moreover, since the medial and intermediate segments of the globus pallidus always receive their blood supply from the anterior choroidal artery, except in those rare cases in which the artery is vestigial, and since the globus has a great paucity of capillary circulation, this structure is peculiarly vulnerable to anterior choroidal artery occlusion.

One other essential fact had to be determined; that is, the relative constancy of this artery. In this regard, Abbie had found that in no case, in a series of 80 cerebral hemispheres examined, was it impossible to find a vessel which had the origin, course, and distribution of the anterior choroidal artery—although variations of mode of origin occur. All of Abbie's findings were confirmed and extended in Alexander's masterly investigation. On the basis of these anatomic data and our experience with 1 case of unplanned anterior choroidal artery occlusion, it was decided that a deliberate attempt to occlude this vessel in far advanced cases of parkinsonism was justified.

SELECTION OF PATIENTS FOR OPERATION

During the early phases of this investigation the following criteria were established for selection of patients for operation:

1. The presence of far advanced parkinsonism of long standing.
2. Complete intractability of the signs and symptoms of this disorder to all known medications and conservative therapy.
3. Total incapacitation as regards earning a livelihood or self-care.
4. Full understanding of each patient and his family of the investigative nature of the procedure as well as the hazards which are involved.

At the outset of this study, one could not be certain which age groups and which type of parkinsonism would be best suited to this type of operative intervention. Therefore, the pilot study included a wide range in age, with patients who varied from 36 to 88 years of age, and also included the three major types of parkinsonism; that is to say, postencephalitic, idiopathic, and senile or arteriosclerotic.

It became readily apparent during the early phase of this investigation that the hazards of this type of surgery are greater in patients over 60 years of age. Therefore the senile or arteriosclerotic type of parkinsonism was early eliminated, and only cases of postencephalitic or idiopathic parkinsonism were considered for selection for operation during the latter phase of this pilot study.

More precise indications for selection of patients have become apparent as a result of this study and will be covered later in the course of this presentation.

METHOD OF INVESTIGATION

A system of cross-check examination by many disinterested examiners was set up and, insofar as possible, the criteria for assessing therapy in Parkinson's disease set forth by Schwab and Prichard were rigidly adhered to.

Each patient in this series had been examined preoperatively and postoperatively by at least 4 disinterested, qualified examiners. Moreover, the observations of the patient, members of his family, attendants, nurses, and technicians regarding tremor, rigidity, speech, swallowing, disability, and other factors were recorded and form part of the investigation.

Cinematographic records were made before and after operation of many of the patients in the series. These, too, have been studied by disinterested examiners.

Follow-up examinations are made when possible every week for 3 months, then monthly until the sixth postoperative month, and then bimonthly until the first postoperative year is completed.

TECHNIQUE OF OPERATION

Prior to operation bilateral carotid arteriography is performed in order to visualize each anterior choroidal artery, and to rule out the presence of anomalies of the circle of Willis. The origin, size, course, and relations of the vessel are thus appraised. Knowledge of the relationship of the anterior choroidal artery to the posterior communicating artery is particularly valuable at the time of operation, and can be obtained from arteriography in most instances (Fig. 1).

Originally, a frontotemporal approach was employed with dissection along the sphenoid ridge to identify the internal carotid artery (Fig. 2). This approach was satisfactory in most respects, but it was often necessary to rotate the internal carotid artery in order to adequately visualize its anterior choroidal branch. This manipulation of the internal carotid produced visible spasm of the branches of the circle of Willis. Therefore, at the suggestion of Poppen and of Mount, a subtemporal approach was employed and has proved eminently satisfactory.

Operation is now performed with the patient placed on his side, the side of operation remaining uppermost. The uppermost limit of the operating table mat is at the level of the shoulder, thus allowing the head to hang down onto the headrest (Fig. 3). This permits the dependent cerebrum to be partially elevated from the floor of the cranium. Spinal fluid drainage by the lumbar route is used. A subtemporal craniectomy approximately the size

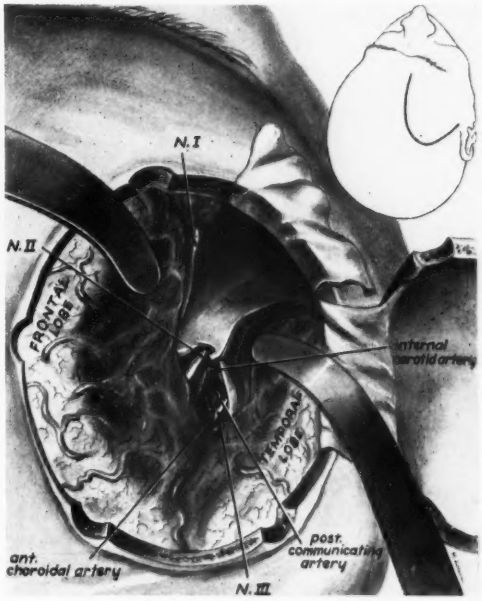

Fig. 2. Original operative approach to the anterior choroidal artery through a frontotemporal craniotomy.

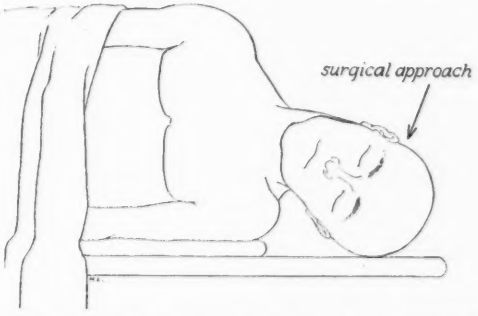

Fig. 3. Position of patient on operating table when the subtemporal approach is to be employed. The dependent position of the head allows the temporal lobe to be elevated from the floor of the temporal fossa with minimal retraction.

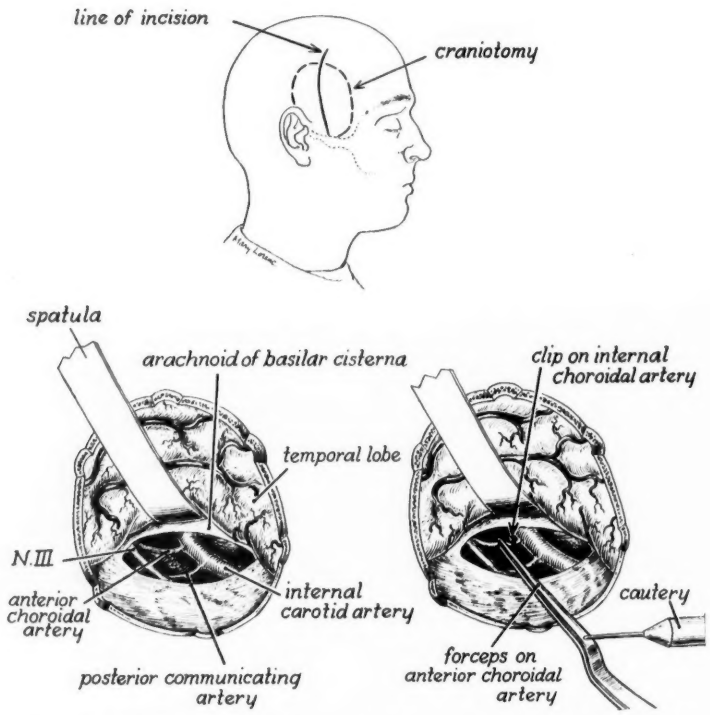

Fig. 4. Diagrammatic representation of subtemporal approach to the anterior choroidal artery. a, Site of incision and craniectomy. b, Elevation of temporal lobe to allow visualization of basilar cistern and its contents. c, Occlusion of the anterior choroidal artery by silver clip and by electrocauterization.

of a silver dollar is made (Fig. 4). The dura is opened and the temporal lobe is gently elevated. When the edge of the incisura of the tentorium is reached, the arachnoid of the basilar cisterns is visualized and opened. One then immediately recognizes the oculomotor nerve and internal carotid artery with its posterior communicating and anterior choroidal branches (Fig. 4b). The posterior communicating may be followed to its origin with the posterior cerebral artery, and at least 1 centimeter of the anterior choroidal artery is easily seen. The anterior choroidal artery is obliterated as close to its origin as possible by silver clips. It is then necessary to destroy the vessel for at least 1 centimeter of its course by electrocoagulation (Fig. 4c). This is necessary for two reasons: first, to insure the fact that the vessel has been obliterated; and, secondly, to destroy the vessel beyond the point of emergence of its pallidal branch and thus obviate the possibility of retrograde collateral supply from the posterior choroidal branches of the posterior cerebral artery (Fig. 5). The necessity for this carefully executed electrodesiccation of the vessel cannot be overemphasized.

These patients tolerate anesthesia poorly, and extremely light anesthesia should be used. Our patients are induced and intubated under cyclopropane. They are then maintained on nitrous oxide and oxygen combined with a dilute infusion of pentothal. Not more than 100 to 200 milligrams of the latter are used throughout the entire procedure. Hypotensive anesthesia is to be avoided in these cases. Prior to clipping and coagulation of the anterior choroidal artery, a continuous

intravenous infusion of papaverine or paveril, 15 grams in 1,000 cubic centimeters of 5 per cent glucose, is started. This is continued into the postoperative period. It is our impression that this drug helps to prevent spasm of the internal carotid artery and its branches when administered in this fashion.

POSTOPERATIVE CARE

A detailed outline of postoperative care is not herein indicated. Certain facts, however, are worthy of emphasis. Patients with parkinsonism are prone to have neurovegetative abnormalities, and meticulous fluid balance studies and temperature regulation are required. In patients who are somnolent postoperatively, continous intravenous infusions of benzedrine, 80 milligrams in 1,000 cubic centimers of 5 per cent glucose, are used, and gavage feedings are instituted the second day. Since excessive salivation and dysphagia are commonly seen in the postoperative period, early tracheotomy is warranted in some cases to obviate the danger of aspiration. Constant, vigilant nursing care is of the utmost necessity, since these patients, who are helpless prior to surgery, are further depressed by the operation and thus are particularly dependent during the immediate postoperative period.

RESULTS

A statistical analysis of the results in a limited pilot study of this type is impossible and would be meaningless. Significant results, however, have been encountered often enough to be meaningful and are herein summarized. Our experience with arteriosclerotic type of parkinsonism is limited to 2 patients, neither of whom survived the postoperative period. Both of these patients died suddenly on the third postoperative day. The cause of death in these elderly individuals is not yet clear. We concluded that the hazards of this approach in patients over 60 years of age were too great to warrant extension of the study in this group.

The most strikingly favorable results were seen in the postencephalitic type of parkinsonism. Similar, but less marked, effects were observed in the idiopathic type of disorder.

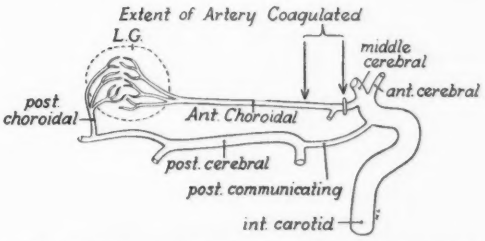

Fig. 5. Diagrammatic drawing of anterior choroidal artery demonstrating its origin from the internal carotid artery and potential source of collateral supply from posterior choroidal system. The necessity for destruction of the proximal portion of the vessel to prevent it from receiving blood either from the internal carotid or posterior choroidals is evident. This procedure, however, will not interfere with collateral blood supply to the lateral geniculate body.

The effects recorded will be noted in the following and then illustrated in a few case reports.

Tremor. Resting, alternating type tremor, which is confined to the distal parts of the extremities and which disappears during voluntary motion has been lessened or abolished in 9 out of 11 postencephalitic cases in which the procedure was performed. In 4 of these cases this type of tremor has been completely absent from the affected extremities since operation. One of these cases now has been followed over 1 year. The other 3 cases, in which tremor was completely alleviated, have been followed 9, 8 and 7 months, respectively.

Ataxic tremor, or tremor persisting through motion, has *not* been affected by this procedure. Patients in whom ataxic type tremor is the principal complaint should not be subjected to anterior choroidal artery occlusion.

Rigidity. The most constant, significant, and striking effect of anterior choroidal artery occlusion has been the relief of long-standing, incapacitating rigidity. In certain cases, patients who were virtually immobile and bedridden because of rigidity have been free of any incapacitation due to rigidity since operation. Cogwheelism and other objective manifestations of rigidity have been noted to disappear. The most favorable results in this regard have been in the postencephalitic cases. Certain patients who were completely dependent and helpless due to rigidity are now

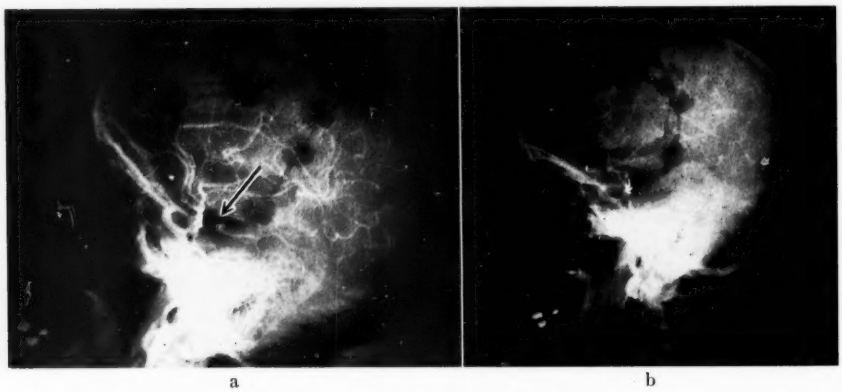

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Fig. 6. a, Right carotid arteriogram in Case 1 demonstrating failure of silver clips to occlude right anterior choroidal artery, designated by arrow. b, Right carotid arteriogram followed reoperation with successful occlusion of the anterior choroidal artery.

capable of self-care in feeding, dressing, and other daily necessities.

In 2 cases, marked dystonic deformities due to rigidity have been noted to disappear gradually following alleviation of rigidity by operation. Improvement in certain spheres of activity has been progressive for as long as 1 year following operation.

Rather remarkable improvement in speech, gait, masked facies, poverty of automatic movements, and swallowing have been noted in certain patients. All of these improvements are probably secondary to relief of muscular rigidity. Examples of such improvement are illustrated in the following case reports.

CASE REPORTS

CASE 1. W.T., a 36 year old white male, developed rigidity and tremor of postencephalitic parkinsonism at the age of 18 years. This disorder was progressive so that by the age of 28 years he was incapacitated and was hospitalized at Kings County Hospital where he remained for 18 months. In 1949 he was studied at the New York University-Bellevue Rehabilitation Center. It was decided that rehabilitation was impossible because of complete incapacitation due to parkinsonism. Later, in 1949, he was admitted to Central Islip State Hospital for domiciliary care. By this time he was relatively vegetative and was relegated to the back wards until his admission to our service in January, 1953.

Our examination revealed an emaciated white male confined to bed. The facies was masklike. There was boardlike rigidity and a typical pill-rolling, alternating tremor at rest. There was also a tremor which persisted through motion and which became violent during excitement, involving all extremities, head, neck, and trunk. The patient had to be lifted into a wheelchair. He could not stand alone because of his severely flexed posture. He could not walk, nor could he feed himself, wash, hold a book to read, or hold a pen to write. Speech was barely perceptible.

In February, 1953, the left anterior choroidal artery was occluded by silver clips. The postpoerative course was marked by significant lessening of rigidity and tremor in the right extremities. Rigidity, cogwheelism, and tremor were estimated to be 90 per cent decreased on the right but unchanged on the left. There was no motor weakness. However, the patient was quite somnolent and lethargic for the first 2 weeks following surgery.

In March, 1953, two silver clips were placed on the right anterior choroidal artery. Following this procedure we noted absolutely no change in rigidity or tremor of the left extremities. Therefore, a left carotid arteriogram was performed, and this demonstrated that the clips had not completely occluded the anterior choroidal artery (Fig. 6a). Accordingly, reoperation through the same route was carried out, and the silver clips were crushed tightly, thus definitely occluding the anterior choroidal artery (Fig. 6b). This was followed by immediate dampening of tremor and rigidity of the left extremities, with further improvement on the right side as well. From that day to the time of this report, there has been progressive improvement in this patient's status.

The most striking feature has been return of useful motor power due to alleviation of rigidity and its attendant disabilities. On the fourth postoperative day the patient lifted himself to a sitting position in bed. The following day he walked unassisted, and produced his first written word in many years.

During the next several months the patient demonstrated progressive improvement. Whereas he had required constant bedside nursing care, he became completely independent in self-care. He could soon feed, clothe, and bathe himself and attend to all bodily needs. Within 2 months after surgery, he played both golf and baseball on the hospital grounds. By the third postoperative month he was working as a gardener in the hospital maintenance corps. He was evaluated by Dr. F. J. O'Neil and his associates under whose care the patient had been since 1949, as well as by the nurses and attendants who had cared for him. All of these independent evaluators concurred in the opinion that the patient was remarkably improved. The progressive improvement of this patient following surgery is documented in successive letters written by him.

In December, 1953, he was returned to the New York University-Bellevue Rehabilitation Center for re-evaluation. He was also presented to a group of 25 neurologists and neurosurgeons to whom he demonstrated his ability to speak intelligibly, walk without festination, perform rapid movements, write, do 10 consecutive push-ups and swing a golf club. His evaluation by Dr. H. A. Rusk's service was as follows:

Mr. M. E. McCavitt, vocational therapist, stated: "The patient is a 37 year old man who had been disabled for 19 years, 15 of which he was largely a wheelchair patient . . . He now speaks with clarity and understanding and has little or no rigidity. Coordination is good. He is completely self-sufficient in all activities of daily living, and feeds himself, shaves, and is able to socialize freely. He is very enthusiastic about his improvement and constantly demonstrates his grip, rapid flexion movements, etc. With instruction, he will probably make considerable further gains in speech, handwriting, and his over-all ability to communicate."

In order to enable us to evaluate the effect of operation, no rehabilitative therapy was instituted until the patient had completed one full year following surgery. Since this time has now elapsed, the patient has been accepted on the Rehabilitation Service and is receiving on the job training as a plumber's assistant.

Case 2. A. T., a 59 year old white male, was referred to our service by Dr. Anthony Desti who stated in his referring letter, "I wish to refer a patient who has been a helpless cripple for the past 17 years."

This patient had been forced to give up work as a barber in 1936 due to tremor and rigidity of postencephalitic parkinsonism. During the ensuing years he became increasingly incapacitated and was hospitalized for long periods at Kings County Hospital, Presbyterian Hospital, and Flower Fifth Avenue Hospital, respectively. At the latter hospital in 1947, the following note was recorded by Dr. A. Akelaitis, "The patient is bedridden, with mouth open and infrequent blinking of the eyes. There is considerable tremor of all extremities, which is worse on the left and which is coarse and aggravated by the examination. There is cogwheel-like rigidity of all extremities and movements are slow."

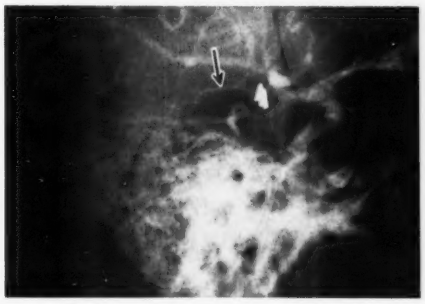

Fig. 7. Right carotid arteriogram in Case 3 demonstrating patency of anterior choroidal artery despite presence of 3 tightly occluded silver clips on the vessel. The artery was subsequently occluded at reoperation by electrocauterization.

The patient was treated with bella bulgaris and improved enough to walk about the wards unassisted. However, the effectiveness of this medication subsided and the patient was discharged unimproved. He remained unimproved by other medical therapy.

Our examination, in June 1953, revealed an elderly man who was completely incapacitated and required constant nursing care. The facies was masked and speech was barely audible. Rigidity of all extremities was boardlike. There was a moderate, bilateral, resting-type, pill-rolling tremor. The patient could not walk alone, feed himself, or perform any of the ordinary activities of daily living.

In July 1953, the right anterior choroidal artery was occluded by silver clips and by electrocauterization. Artane and stramonium, which he had been taking, were discontinued prior to surgery. He has received no drug since, other than benzedrine during the first 3 months following operation. During the first 3 weeks following surgery he was very lethargic and somnolent, but this tendency gradually subsided. Rigidity and tremor have been absent from the left extremities since the time of surgery. Moreover, there has been progressive improvement in gait, speech, self-care, and all activities of daily living since that time. The improvements noted in this patient are documented in letters from the patient's wife during the fourth, fifth, and sixth postoperative months. In these letters, she stated: "My husband is a different man. For the past 10 years he was completely helpless; now, he can do anything for himself. Before his operation, he was so rigid that he remained like a statue; he had to call me to change his position. When he tried to move, his tremors became violent. He could not walk alone. When he walked with our assistance, his hands stayed close to his body without moving. Now he walks straight,

a b

Fig. 8.

Fig. 8. Marked change in facies following occlusion of right anterior choroidal artery in Case 3. a, Markedly masked facies of long standing preoperatively. b, Note change in expression 4 months after operation. Note also the lessening of rigidity in left orbicularis oculi muscles and left sternocleidomastoid.

Fig. 9. Change in posture and flexion deformity of left upper extremity following occlusion of right anterior choroidal artery. a, Condition preoperatively. b, Change in posture and deformity 4 months after operation.

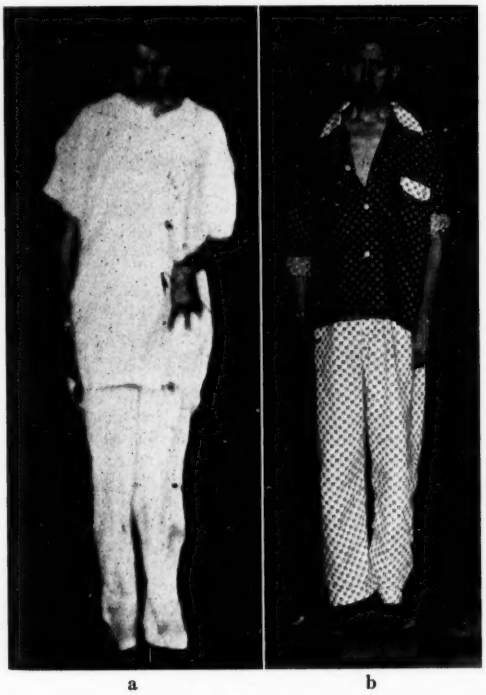

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Fig. 9.

alone, and his left hand swings. For 12 years he could not shave, or feed or dress himself; now, he does all of these things. He was so rigid before, he needed three pillows in bed; now he uses only one pillow. He smiles again now and is relaxed and his speech is clear. He cleans the house, cooks, and waxes the floor. For the first time in 12 years, he was able to go out to a restaurant to eat and to sit 3 hours afterward in a movie. We went to a party and he took his guitar and played it."

Mr. M. E. McCavitt examined the patient for evaluation for vocational rehabilitation during the sixth postoperative month. At that time he stated: "This patient who has been ill for 18 years now walks well. There is no tremor on the left and little obvious tremor on the right. He smiles and is able to discuss his improvement with much insight. He takes great pride in the fact that he took his wife to Radio City recently and that he is able to play a guitar and can feed, shave, and dress himself."

During the eighth postoperative month he was re-examined by Dr. Akelaitis, whose prior findings are reported in the foregoing. He stated: "The striking change from his previous status is the presence of associated movements in the left upper extremity and the absence of cogwheel rigidity in the left upper extremity. In fact, tonus in the left upper extremity seems normal to passive movement. No tremor is evident in the left upper extremity and patient can do fine movements with the left hand."

Case 3. W. D., a 41 year old white male, was referred for consideration of anterior choroidal artery occlusion by Dr. Walter Freeman. In his written summary of this case, Dr. Freeman stated, "This patient contracted epidemic encephalitis at age 15 and was in coma for 6 weeks. Within 1 year, tremor and rigidity occurred and he was soon incapacitated. He never returned to school and the incapacitation has progressed steadily. At present he cannot stand alone because of severe retropulsion, and he can walk only with assistance. He cannot get out of a chair alone and cannot get up from a lying position. When he sits unsupported, he has to be held by his hand or supported from the back. He cannot feed himself because of the very considerable rigidity. He can swallow only soft, mashed foods and must be fed lying down. Examination reveals a masklike face, with the mouth open and considerable tremor of the tongue with a clacking noise which goes on almost continuously, but can be controlled for a moment or two. The patient is almost speechless, but occasionally can issue a grunt or two. What words there are are incomprehensible because of such rigid slurring. The left upper limb is in flexion at the

elbow, shoulder, and wrist with extension of the fingers and very marked cogwheel phenomenon and gross rhythmic tremors that can hardly be suppressed. The right upper limb shows a greater degree of flexibility and can be used for gross movements but not for fine movements. It is likewise affected by a constant tremor which can be halted occasionally. The lower limbs show considerable rigidity with little tremor. I am not optimistic about the outcome in this case since the disease is of long standing with great deformity and disability."

This patient had been attended by trained nurses since the onset of disability 26 years previously.

On September 2, 1953, a right frontotemporal craniotomy was performed and 3 silver clips were applied to the anterior choroidal artery. No change in tremor or rigidity were noted during the ensuing week, and the procedure was considered a failure in this instance. Therefore, 8 days following surgery, a right carotid arteriogram was performed. This demonstrated the fact that the anterior choroidal artery passed through the clips but had not been occluded (Fig. 7). Therefore, reoperation was performed and on this occasion the anterior choroidal artery was obliterated by electrocoagulation. From the time the patient awoke from anesthesia, rigidity and tremor have been absent from the left extremities. Moreover, there has been progressive improvement in gait, speech, swallowing, and all activities of daily living. The most remarkable feature has been complete reversal of what appeared to be a fixed deformity of the left upper extremity which, prior to surgery, could not be moved by strong passive manipulation. The progressive improvement during the postoperative course of this patient is best documented by the following directly quoted sources, and by the related figures.

One month postoperatively, Dr. Walter Freeman stated: "Mr. D. has shown remarkable limbering up of the left upper limb so that the wrist can be almost straightened and the hand is warm and pink. The tremor persists on the right side but not the left. He has made considerable progress but is a long way from being independent."

Two months postoperatively, the patient's father called long distance to state, "W. has continued to improve remarkably. The left hand is completely straight and he can use it. Today he dressed himself for the first time in over 15 years, even tying his own shoe laces and buttoning all buttons."

Three months postoperatively, the patient's sister saw him for the first time since surgery and called to report, "I was amazed to see him. His progress is unbelievable. He goes to the bathroom alone; feeds himself sitting at the table; talks well, although his voice fatigues by evening; and walks very well alone without running forward or falling backward as he did. His left hand is straight and does not tremble a bit. He has gained weight, his cheeks have filled out and he looks like he did 25 years ago. The drawn, tight look is gone from his face. You will be thrilled to see him" (Figs. 8, 9, and 10).

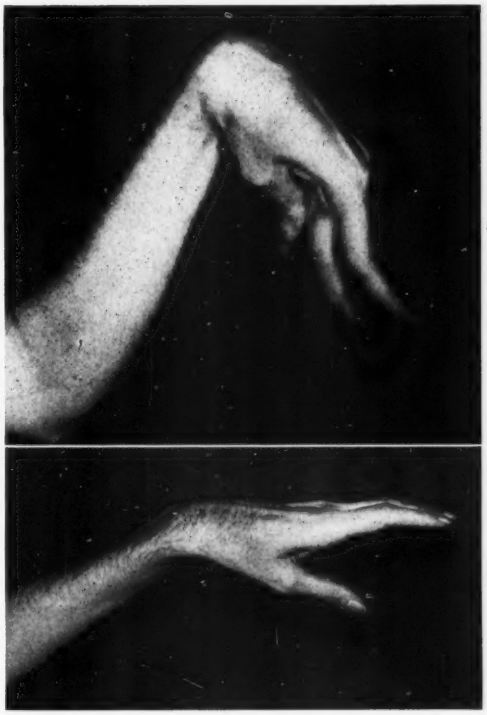

Fig. 10. Longstanding dystonic deformity of left hand in Case 3. The deformity appeared to be fixed and could not be reduced by passive manipulation, even under anesthesia. Note flexion of wrist, extension of fingers at middle interphalangeal joint, and adducted position of thumb. b, Complete reversal of deformity 4 months after operation.

Fourth postoperative month, Mr. Martin McCavitt and Mr. Paul R. Clark jointly evaluated this patient as a candidate for occupational therapy and rehabilitation. They stated: "The patient can speak and could be understood quite well. He can dress himself, feed himself, walk several city blocks alone, and is well oriented and well informed about current events. The left hand shows no tremor, while his right hand has a fine rhythmic tremor which is reduced to a point where he can write legibly. Although the patient has never held a job and has been incapacitated for 25 years, his over-all functional improvement has been remarkable. This patient can become completely sufficient in all activities of daily living, and he appears to be an excellent candidate for rehabilitation. Certain selected vocational opportunities should be explored."

At the time of submission of this report, this patient has been followed for 7 months since operation. The alleviation of rigidity, tremor, and deformity in

the left extremities has persisted, as has improvement in speech, posture, gait, swallowing, and facies. The degree of relief of disability has been marked enough in this case, as well as in Case 2, to enable us to defer indefinitely consideration of operation on the second side. Although the relief of tremor and rigidity was largely confined to the extremities contralateral to operation, the resultant lessening of disability has been sufficient to render these patients, who were previously incapacitated, capable of self-care.

CONFIRMATION BY INDEPENDENT INVESTIGATORS

One essential criterion for evaluating the results of any surgical investigation is the achievement of similar results by independent investigators. Several neurosurgeons have informed me of similar results to those which have been described.

Pool has reported 2 cases, in one of which he performed unilateral operation and in the other, bilateral anterior choroidal occlusion was carried out. The latter case was a 33 year old man who had been completely helpless for 12 years due to postencephalitic parkinsonism. He was so rigid that he could not initiate any movement. He had a moderate, pill-rolling tremor bilaterally, marked masking of the facies and speech was barely audible. His sister stated that he was 100 per cent dependent and required constant care by herself and an attendant. Five months following operation by Doctor Pool, the same sister stated, "He is now fully independent; he feeds himself, bathes himself, and can get out of a deep couch that a normal person would have trouble with. He can walk several miles, has no tremor, and his facial expression is normal again. He was taking artane before the operation but has taken no medication since. He has been improving constantly since the operation, and is able to drive a car."

MacLean has 3 cases with marked improvement. Hoen, Gardner, Walker, Fairman, and Bertrand have each had successful results with anterior choroidal artery occlusion, although the degree of success and the period of follow-up varied. Bertrand's case was demonstrated during the follow-up period at a meeting of the Montreal Neurologic Society and was considered to have shown remarkable improvement. In each case, as in those of the author, the most striking and beneficial effects were due to alleviation of rigidity, which was previously intractable, without the loss of any motor power.

COMPLICATIONS

The surgical mortality rate during this pilot study has been 13.3 per cent. There is reason to believe that this figure will be significantly lower if the proper criteria for selection of patients, which have evolved during the course of this investigation, are rigidly adhered to. There has been no mortality in the last 10 consecutive cases of anterior choroidal artery occlusion.

Two instances of postoperative hemiplegia were encountered in the first 30 operations. One of these patients subsequently died and at necropsy a cerebral infarct was demonstrated in the left cerebral hemisphere in the entire distribution of the middle cerebral artery. The pathogenesis of infarction in the distribution of the middle cerebral artery following surgical occlusion of the anterior choroidal artery is not entirely clear, although several possible mechanisms are being investigated at the present time.

Three cases of oculomotor nerve palsy occurred, which were probably due to direct trauma at operation. Each of these has cleared spontaneously.

OTHER NEUROLOGIC OBSERVATIONS

Several neurologic observations which have been made following anterior choroidal artery occlusion deserve mention. The most common side effect noted during the postoperative period has been somnolence. This varies from sleepiness to stupor and lasts from 1 to 10 days. We now use benzedrine by continuous intravenous infusion to counteract this tendency during the immediate postoperative period and continue the drug orally for several weeks following operation.

In 2 cases, we noted anhydrosis of the ipsilateral face, trunk, and extremities for 10 days following operation.

Two patients demonstrated lip smacking movements for 1 week after operation. One of these patients had formed visual hallucinations during the same period. He was aware

of the hallucinatory nature of these visions when they occurred. Two patients were noted to have mild memory defect for recent events for a few weeks following surgery. All of these phenomena proved to be transitory.

Gross confrontation visual field examinations were made before and after operation in every case. Detailed visual field studies were charted in 12 cases, before and after operation. In no instance has any visual field defect been observed postoperatively. This is considered to be due to the rich vascular anastomoses from the posterior cerebral artery over the lateral geniculate body. The operation is designed to permit collateral circulation from this source to reach the lateral geniculate but to prevent it from reaching the globus pallidus.

Electroencephalographic tracings have been obtained before and after operation in each case. In most instances, there has appeared postoperatively a delta focus occupying the frontomotor and posterior temporal areas. In 2 cases there was also spike activity in the contralateral frontal area.

It may be significant that 3 patients volunteered the information that constipation of many years' standing disappeared following relief of rigidity. This finding has also been noted by MacLean in his series.

A detailed evaluation of neurologic, electroencephalographic, and neuropathologic effects of anterior choroidal artery occlusion is in progress.

DISCUSSION

One must consider the results of this investigation from two standpoints: First, what are the immediate practical results of anterior choroidal artery occlusion and what is its place, if any, in the treatment of parkinsonism? Secondly, what are the basic neurophysiologic implications involved in these observations?

The practical considerations shall be considered first. The results of anterior choroidal artery occlusion reported in the foregoing, as well as the confirmation of satisfactory results in the hands of several independent investigators, would appear to warrant the conclusion that this operation is capable of affording relief of disability in selected, far advanced, incapacitated cases of parkinsonism. Moreover, such relief has thus far been demonstrated to endure for at least 1 year. The specificity of the operation is attested to by the 2 cases cited in which application of silver clips to the anterior choroidal artery without occluding the vessel failed to affect contralateral tremor and rigidity; whereas, subsequent identical operation with obliteration of the vessel produced a profound effect. These 2 instances serve as excellent "control" experiments. In addition, the fact that improvement in each successful case was objectively demonstrable to many examiners, and was concrete enough to be translated into definite terms of improved function, documents the effect of this procedure in certain cases. The experience with this operation thus far indicates that the cases best suited for selection are postencephalitic patients chiefly incapacitated by rigidity, in whom any tremor present is of the resting variety confined to the distal portions of the extremities, the face, and lips. Idiopathic cases have also benefited, but not as markedly as the postencephalitic group. It is preferable that candidates for surgery be under the age of 50. However, one of the most successful results was seen in the case of the 59 year old man cited. Senile or arteriosclerotic cases constitute too great a hazard for this procedure at present.

In the properly selected case, there would appear to be a reasonable chance of alleviating not only resting tremor and rigidity but also of favorably affecting speech, facies, swallowing, automatic movements, posture, and gait, as illustrated in the cases cited as well as in the cases of Hoen, Pool, Fairman, MacLean, and others. Moreover, the follow-up studies to date have been encouraging in that certain of the patients have shown progressive improvement for many months following surgery.

By no means has enough data been accumulated to enable one to state in what percentage of cases of far advanced parkinsonism anterior choroidal artery occlusion will be successful, or whether good results will endure beyond 1 year. Our only conclusion in this regard is that further careful investigative use

of this procedure is justified by this initial pilot study. The ultimate practical value of the procedure cannot yet be ascertained. Although an attitude of cautious hopefulness is engendered by the confirmation of these results and by the present knowledge of proper selection of patients, three principal facts must now be learned. These are: (1) The long term follow-up results of at least 2 to 5 years; (2) the percentage of cases that will benefit from operation if the criteria for selection set forth are rigidly adhered to; (3) the statistical analysis of improvement, morbidity, and mortality in a large series of properly selected cases.

Only additional time and objective study will afford the answers to these questions. Failures, when encountered, must be as carefully documented as successful cases if a factual evaluation is to be achieved. As illustrated in Cases 1 and 3 of this report, postoperative arteriography should be performed to check for complete occlusion of the vessel, if the operation is not successful.

While the data essential to further practical evaluation are being accumulated, one must consider the neurophysiologic implications of these observations. The role of the globus pallidus and other related structures affected by anterior choroidal artery occlusion in the pathogenesis of tremor and rigidity requires elucidation. Moreover, the investigative technique of planned infarction by vascular occlusion may be of use in other situations. Meyers has previously demonstrated, in his investigation of pallidofugal section, that tremor and rigidity can be relieved without sacrificing motor power. Perhaps the most material fact to come out of this study is the demonstration and confirmation by several investigators that far advanced signs and symptoms of parkinsonism, including seemingly fixed deformities, are reversible without sacrifice of motor power. The conclusive demonstration of such reversibility should encourage further investigation to be carried out in the therapy of advanced hyperkinetic disorders.

SUMMARY AND CONCLUSIONS

1. The rationale and anatomic basis of anterior choroidal artery occlusion in parkinsonism, as well as operative technique, selection of patients, favorable results, and complications which occurred in a pilot series of 30 operations have been reviewed in this presentation.

2. In certain far advanced, incapacitated cases of parkinsonism, occlusion of the anterior choroidal artery has been followed by significant alleviation of resting tremor and rigidity in the contralateral extremities. Improvement in speech, swallowing, masked facies, posture, and gait have been noted in several cases. Progressive improvement following operation has enabled several incapacitated patients to become independent in self-care.

3. The most favorable results of anterior choroidal artery occlusion have been noted in patients with postencephalitic parkinsonism, who were principally incapacitated by rigidity.

4. The ultimate usefulness of this procedure can be evaluated only by longer term study of properly selected patients. However, on the basis of the results of this investigation, further practical inquiry into the effect of anterior choroidal artery occlusion in cases of far advanced parkinsonism would appear to be justified.

ADDENDUM.—The results of this procedure have become increasingly satisfactory during the months since this report was originally prepared. Moreover, no patient in whom the anterior choroidal artery was properly obliterated has had recurrence of symptoms.

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HEPATIC CHANGES OCCURRING DURING UPPER ABDOMINAL OPERATIONS: BIOPSY STUDIES

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STUDY of pathologic alterations in the human liver is based chiefly upon examination of three types of material, namely that seen at necropsy, that obtained during needle biopsy, and that comprising the surgically removed specimen. The agonal variations that occur in material examined at necropsy have been studied and presented clearly by Popper. The differences between material obtained by needle and at laparotomy have not been widely studied, however. From a purely technical angle, Mateer and associates were of the opinion that the needle often bypassed some of the fibrous tissue found during surgical biopsy. Keller and Smetana, on the other hand, considered that a truer picture was presented by needle biopsy, for such material was free from surface artifacts. They described these artifacts as: (1) accumulations of polymorphonuclear leucocytes in zones of focal necrosis of hepatic cells, (2) subcapsular infiltration of neutrophils, and (3) subcapsular and parenchymal hemorrhages. They suspected that these alterations were the result of trauma or the presence of a nearby inflammatory process. Mateer and his group described this polymorphonuclear leucocytic infiltration in their series of surgical hepatic biopsies but did not see any concomitant cellular necrosis and were not sure of its cause.

It is well substantiated that impairment of hepatic function frequently occurs as the result of an operation. Therefore, the present study was undertaken to compare the appearances of material taken for biopsy at different times during operations and to observe any changes that might be produced by factors operating as a result of the surgical procedure itself. This was done in conjunction with studies in a larger series of surgical biopsies of normal livers, the results of which are being published elsewhere by us (1). The present study is concerned chiefly with the polymorphonuclear leucocytic response as seen in the livers of patients during operations on the upper part of the abdomen.

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MATERIALS AND METHODS

Hepatic biopsies were done at two separate times in patients undergoing operations for various upper abdominal conditions. As soon as the abdomen was opened and the type of operation decided upon, a generous wedge of tissue was taken for biopsy. This procedure was repeated at the end of the definitive operation just before closure of the abdominal wall. All tissue was taken as a deep wedge, usually extending about 1 centimeter or more beneath the capsule and usually away from the edge of the liver. The tissue was sectioned immediately by the fresh frozen technique for routine immediate diagnosis, and the remaining portion was placed in a 10 per cent solution of formalin. Fixed frozen sections were made later and stained with hematoxylin and eosin for use in this study. Paraffin sections were prepared in some instances and special stains were used when indicated. Specimens showing evidence of severe hepatic disease, such as cirrhosis, extensive hydrohepatosis, or metastatic malignant lesions, were discarded from this series, it being our intention to study normal-appearing livers in so far as possible.

A total of 38 patients were included in this study; 22 had duodenal ulcers and 5 had gastric ulcers. Pancreatitis with or without cholecystitis or obstruction of the common bile duct was present in 7 patients. Included also were

2 patients who had obstruction of the common bile duct with mild obstructive jaundice, 1 patient who had uncomplicated cholecystitis, and 1 who required right colonic resection for multiple lipomas with diverticulosis.

Clinical data were collected from the patients' records. Factors connected with the operation itself were gathered from the operative reports of the surgeons, from the anesthesia records, and from personal observations in many cases. Special efforts were directed toward recording the time of biopsy, the region of the liver sampled, and the estimated degree of trauma sustained by the portion of liver selected for biopsy.

All microscopic sections were studied as unknowns, and a record was made of the individual features that each presented. The microscopic features that showed enough variation to be graded with any degree of assurance were fatty metamorphosis, fibrosis, infiltration of the portal triad, evidences of nuclear regeneration or degeneration, and parenchymal polymorphonuclear infiltration. Nodular regeneration, cellular necrosis, cytoplasmic degeneration, proliferation of bile ducts, edema, and activity of Kupffer's cells were not seen in any significant degree in this group of normal livers (Fig. 1). For purposes of this study, fibrosis referred to the amount seen in various portal triads in the section; nuclear regeneration included the presence of double nuclei, large nuclei, great variation in nuclear size in a given portion of the lobule, multiple nucleoli, and variations in nuclear staining; nuclear degeneration consisted mainly of nuclear crenation with occasional pyknosis. Focal necrosis was not taken into account. The changes taking place in the subcapsular zone were considered separately from those seen in the remainder of the specimen, since these were believed to be probably of traumatic origin.

RESULTS

In each case, the early and late biopsies showed about the same degrees of fatty metamorphosis, fibrosis, infiltration of portal triads, and nuclear degeneration and regeneration. As was true in the previously mentioned larger group of normal livers studied, the incidence of cases in which rather extensive fibrosis, portal inflammation, or regeneration and degeneration of nuclei was present approximated 50 per cent. Thus this incidence was not considered to be abnormal. Fatty metamorphosis was not so common but when present was not associated with any particular clinical abnormalities. No change at all was noted in the amount of fat or fibrosis during operation. Some increases were noted in the amount of portal infiltration (a shift from minimal to marked in 3 cases) and in regenerative and degenerative activity (a shift from minimal to marked in 6 cases). However, these changes were not particularly significant. The fact that the degree of portal inflammation in 1 case changed from marked to minimal during operation demonstrates the irregular occurrence of this feature in the different areas sampled.

The most apparent change that took place during the operation was infiltration of polymorphonuclear leucocytes into the parenchyma of the hepatic lobule (Fig. 2). This is the change noted by Mateer and associates and termed "acute infiltrative hepatitis"; it was also described by Keller and Smetana and considered to be an artifact. The latter workers, however, spoke of an accompanying cellular necrosis, which we did not see. In our study, the polymorphonuclear leucocytes were apparent in the sinusoids and in many places were infiltrating parenchymal cells in clusters (Figs. 3 and 4). When fewer leucocytes were present, they often appeared only in sinusoids. Studies with paraffin sections using stains for reticulum served only to confirm the fact that many of these clusters of cells were outside the sinusoids and in the cells. The zones of polymorphonuclear infiltration were usually located around the central veins, although other portions of the lobule were involved at times. Infiltration in the subcapsular spaces exceeded that found in other portions of the sections, as noted by Keller and Smetana.

When the cases were grouped according to the degree of polymorphonuclear infiltration only 11 per cent (4 cases) of the livers exhibited any degree of polymorphonuclear leucocytic infiltration at the beginning of the operation, and in none was the infiltration

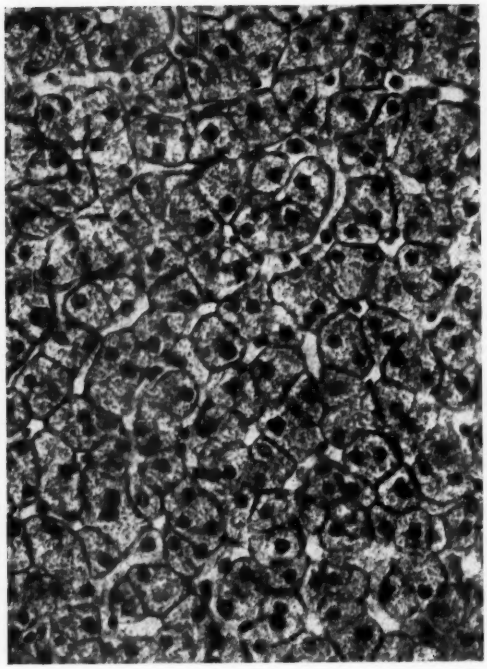

Fig. 1. Minimal alteration of hepatic parenchyma in normal control. Only an occasional doubly nucleated cell is seen. Cellular outlines are distinct. Hematoxylin and eosin, ×350.

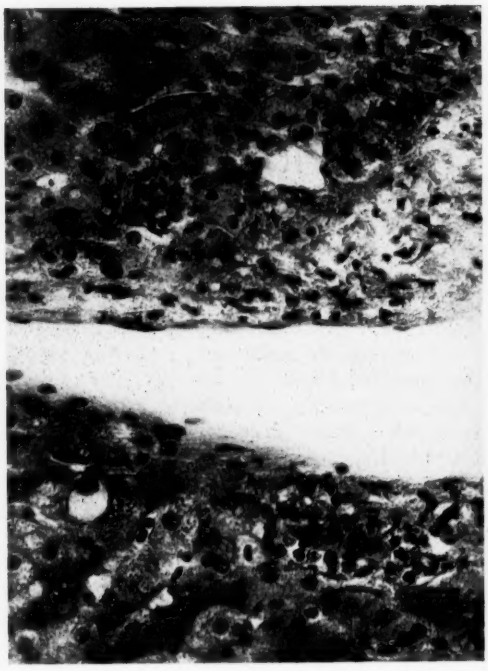

Fig. 2. Minimal polymorphonuclear leucocytic infiltration around a central vein. Although most of the infiltrate lies within the sinusoids, some invasion of hepatic parenchymal cells is noted. Hematoxylin and eosin, ×350.

pronounced. After operation, 34 per cent (13 cases) of the same livers showed marked polymorphonuclear leucocytic infiltration and an additional 40 per cent (15 cases) showed infiltration of lesser degree. There was no polymorphonuclear infiltration in 89 per cent (34 cases) at the beginning of operation and none in 26 per cent (10 cases), after operation. This phenomenon undoubtedly was in some way related to performance of the surgical operation and it becomes understandable how investigators have failed to report the presence of such infiltration in hepatic specimens removed by needle through the intact abdominal wall.

POSSIBLE FACTORS AT OPERATION

After establishment of the fact that polymorphonuclear infiltration occurs in many livers during operations, it remained to attempt discovery of the possible etiologic factors. Our collected data supplied us with information concerning six possibilities, namely: (1) trauma by retractors and manipulation, (2) duration of operation, (3) amount of ether used, (4) amount and type of fluids given intravenously, (5) great decrease in blood pressure, and (6) type of operation.

Trauma. This has been considered by Keller and Smetana to be of prime importance in the production of the changes seen in surgical hepatic biopsies. In most cases, specimens for biopsy are taken from the surface of the liver in the regions that are most exposed to manipulation and trauma from retractors. In 33 of the 38 cases it was possible to obtain some information as to the amount of trauma received by the portion of liver from which the second specimen for biopsy was removed. In 7 of these 33 cases special effort was made to take the specimen from an untraumatized portion of the lobe.

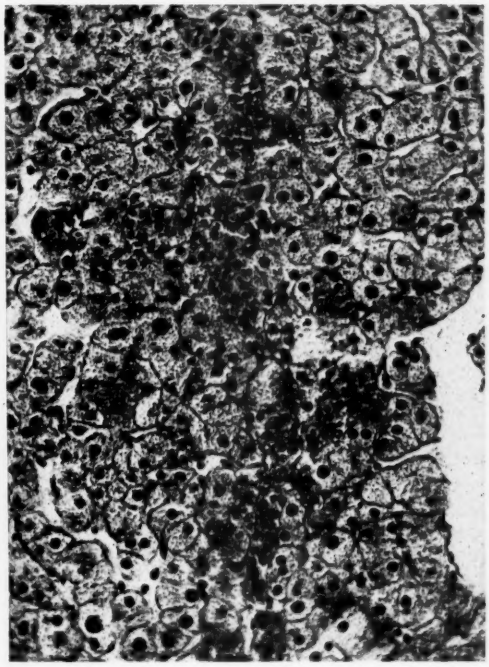

Fig. 3. Marked polymorphonuclear leucocytic infiltration of the liver as seen in tissue which was removed toward the end of an abdominal operation. Hematoxylin and eosin, ×350.

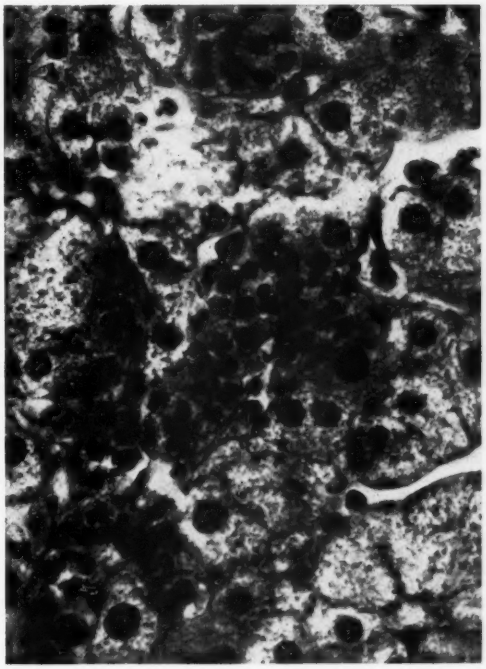

Fig. 4. An area selected from Figure 3 to demonstrate actual invasion of parenchymal elements by polymorphonuclear leucocytes. No necrosis is apparent. Hematoxylin and eosin, ×700.

Among the 26 cases in which the liver was traumatized at operation, 11 (42 per cent) showed a marked increase in polymorphonuclear leucocytes. Conversely, only 1 of the 7 nontraumatized livers (14 per cent) showed a similar increase. We are referring only to those cases in which marked infiltration occurred after operation; the cases in which only a few leucocytes appeared are not included.

Another method of estimating the trauma sustained by the portion of liver from which the specimen is taken is to measure the degree of subcapsular hemorrhage. The obvious objection to this method is that the trauma required in taking the specimen itself might be responsible for the subcapsular hemorrhage. However, it was found that only 6 per cent of the early biopsies showed any subcapsular hemorrhage, whereas 64 per cent of the postoperative group showed this feature. Certainly the same amount of trauma was necessary to take each biopsy. It was considered that this classified hemorrhage as a traumatic change occurring during operation. A tabulation was made in 37 cases, using the presence of subcapsular hemorrhage as a criterion of trauma. Among 13 cases in which no subcapsular hemorrhage was present, 2 (15 per cent) showed an increase in polymorphonuclear infiltration. Conversely, among 24 cases in which marked hemorrhage was present, 12 (50 per cent) showed a similar increase. Thus, both an estimation of trauma and the presence of subcapsular hemorrhage indicate that the amount of trauma received by the liver is related to the presence of polymorphonuclear infiltration.

Duration of operation. This bore little relationship to the development of hepatic polymorphonuclear infiltration. Time relationships calculated on the basis of duration

TABLE I.—CHANGES IN POLYMORPHONUCLEAR LEUCOCYTIC INFILTRATION OF LIVER WITH VARIOUS AMOUNTS OF ETHER

Amount of ether used, ounces	Cases	Marked polymorphonuclear infiltration	
		Cases	Per cent
4 or less	10	4	40
5	7	3	43
6	10	4	40
7	8	1	12
More than 7	3	1	33
Total	38	13	34

of the entire operation, the time between the actual biopsies and the time from the onset of anesthesia to the second biopsy showed no significant correlation with the presence or absence of polymorphonuclear infiltration. If only the time between biopsies was considered, as was done in 32 cases, a slight increase was apparent in the average operating time in those cases in which infiltration was present. However, the average of these times was 1½ hours in the case of the 20 unchanged livers and 1¾ hours in the case of the 12 livers showing marked changes; this is not significant.

Amount of ether used. Ether has been accused of causing hepatic damage. Patients having ether anesthesia alone have exhibited impairment in hepatic function after operations. Since all our patients underwent anesthesia produced by means of nitrous oxide, oxygen, and ether, a comparison was made according to the amount of anesthetic agent used. Table I demonstrates that this factor alone had nothing to do with the development of polymorphonuclear infiltration of the liver. This does not exclude toxic phenomena as possible factors in the production of the infiltrate.

Intravenous administration of fluids. An increased percentage of livers showed polymorphonuclear infiltration in those cases in which fluids were given intravenously. Marked polymorphonuclear infiltration was shown in 2 (20 per cent) of 10 cases in which no fluid was given, 8 (42 per cent) of 19 cases in which dextrose was given, and in 3 (33 per cent) of 9 cases in which blood and dextrose were given. This suggests that the use of such fluids in some way may be related to the production of this change in the liver. However, it must be kept in mind that only those patients undergoing more extensive surgical procedures required intravenous administration of fluids.

Changes in blood pressure. Decrease in blood pressure to levels compatible with shock occurred during operation in 8 cases. In 2 others, a great decrease was noted shortly after the second specimen for biopsy had been taken. Since many consider hepatic anoxia to be a primary factor in the production of shock, the possibility was considered that infiltration of polymorphonuclear leucocytes might have some relation to the conditions prevailing in the liver which were responsible for the decrease in blood pressure. However, analysis of groups with and without extensive decrease of blood pressures did not reveal sufficient differences between these two groups to allow one to suspect any relationship between the appearance of shock and the presence of polymorphonuclear leucocytic infiltration in the liver.

Type of operation. This might be a consideration were it not for the fact that gastric resections were done in 27 of the 38 cases; marked polymorphonuclear infiltration was noted in 10 (37 per cent) of these 27 cases. Operations in 7 other cases were done on the common bile duct, with infiltration in 3 (43 per cent). Various procedures were done in the remaining 4 cases, in none of which was infiltration present.

These findings again suggest the role that trauma may play in the production of leucocytic infiltration. Operations on the common bile duct and gastric resections both necessitate the use of hepatic retractors during a major portion of the procedure. For this reason we compared, among the cases in which gastric resections were done, the 5 cases in which the wedges of tissue were taken from a nontraumatized part of the liver with the 22 cases in which the specimens were taken from zones known to be, or suspected of being, traumatized. Only 1 of these 5 livers showed marked polymorphonuclear infiltration but 9

(41 per cent) of the traumatized livers demonstrated this change.

CORRELATION WITH CLINICAL FEATURES

Not only should factors at the time of operation be considered but also those systemic or local features that conceivably could bear some relation to this hepatic polymorphonuclear infiltration. Our data supplied us with five separate lines of thought, namely: (1) the presence of a systemic inflammatory process, (2) inflammation of the portal triads seen in the same specimens of liver, (3) the condition of the gallbladder, (4) the presence of abnormal results of studies of hepatic function, and (5) variations in sex and age of the patients.

Systemic inflammatory processes. The degree of such processes can be roughly estimated in many patients by the increases in leucocyte counts or the erythrocytic sedimentation rates. Mateer and co-workers noted that leucocytosis was present in a large number of their cases in which such hepatic polymorphonuclear infiltration occurred and they suspected some relationship. In our series, marked infiltration was present in 7 of 17 cases (41 per cent) in which the leucocyte count or the sedimentation rate or both were increased, whereas such infiltration was present in 6 of 19 cases (32 per cent) in which the leucocyte count and sedimentation rate were within normal limits. This is not a significant difference, and thus the presence of a systemic inflammatory process would not appear to be an influencing factor.

Inflammation of the portal triads. This is manifested largely by infiltration with lymphocytes. It is present frequently and cannot be considered as greatly abnormal, although it does accompany such hepatic abnormalities as ductal obstruction. In our series, correlation of this infiltration around the portal triads with the appearance of polymorphonuclear infiltration around the central veins showed no relationship between the two processes, for the livers in which portal inflammatory infiltration was great showed no significantly higher incidence of polymorphonuclear reaction than did the so-called normal livers.

TABLE II.—CHANGES IN POLYMORPHONUCLEAR LEUCOCYTIC INFILTRATION OF LIVER WITH AGE AND SEX OF PATIENT

Sex	Age, years	Cases	Marked polymorphonuclear infiltration	
			Cases	Per cent
Male	50 or less	13	3	23
	More than 50	14	5	38
Female	50 or less	7	3	43
	More than 50	4	2	50
Total		38	13	34

Condition of the gallbladder. Mateer and associates and Keller and Smetana mentioned that nearby inflammation may be in some way responsible for the hepatic polymorphonuclear infiltration. Information was available as to the condition of the gallbladder in only 19 of our series of cases. No significant difference in the incidence of such infiltration was noted, regardless of whether the gallbladder had been removed previously, was normal, was nonfunctioning, or contained stones. Therefore, the presence of disease of the gallbladder did not result in a greater incidence of polymorphonuclear infiltration. No cases of acute cholecystitis have been included in this series, but among the livers in 6 cases of subacute cholecystitis in the larger series referred to previously only 1 showed significant polymorphonuclear infiltration.

Studies of hepatic function. Results of such studies were available in 17 of our 38 cases. Abnormal results of mild degree in one or more tests were present in only 3 cases. Marked polymorphonuclear infiltration was present in the liver in 1 of these 3 cases, whereas it was present in 4 of the 14 cases in which tests of hepatic function showed no abnormalities. Thus, there is no evidence that impaired hepatic function aided in producing this reaction in the liver, although the number of cases is too small to allow adequate judgment.

Sex and age of patients. The relationship of hepatic infiltration to age and sex of the patients is shown in Table II. Although the numbers are small, they show a tendency for this infiltration to occur more frequently in women and among older patients. The significance of this observation is not known.

COMMENT

Surgical hepatic biopsy has certain limitations in study of the microscopic appearance of the liver, as does needle biopsy. The two chief objections to the former method are: (1) inclusion of bits of hepatic capsule, although specimens can be taken rather deeply to include several lobules, and (2) ignorance of how cellular changes reflect the altered physiology of the liver in its response to use of anesthetic agents. It appears from this study that since changes do take place in the microscopic appearance of the liver as a result of operations, it is always wise to take specimens for biopsy as soon as the abdomen is opened.

The significance of polymorphonuclear leucocytic infiltration of the hepatic parenchyma probably is not great. Popper has stated that the normal response of the liver to necrosis is lymphocytic infiltration, whereas polymorphonuclear leucocytic reaction occurs more often as a result of toxic phenomena. However, polymorphonuclear infiltration may occur in almost any tissue subjected to local trauma, and the liver appears to be no exception. This study does not show how far this process may extend throughout the liver, since the specimens were taken from the hepatic surface. In view of the apparent relationship to trauma, it would be surprising if major infiltration occurs deep within the hepatic substance. Further study with deep needle biopsy done at the time of operation will be necessary to clarify this point.

As far as we can determine, the microscopic changes that occur in the liver during operation are not clinically significant and probably have little bearing on postoperative impairment of hepatic function. Our study leads us to agree with Keller and Smetana that both subcapsular hemorrhage and polymorphonuclear infiltration of the liver are traumatic artifacts.

SUMMARY AND CONCLUSIONS

A study was made at the Mayo Clinic of specimens of liver taken for biopsy at the beginning and again at the end of operations on 38 patients who did not have hepatic disease.

The degree of fatty metamorphosis and fibrosis was unchanged during operation, whereas a slight increase occurred in the amount of portal inflammation and in nuclear regeneration and degeneration.

Polymorphonuclear leucocytic infiltration of the central zones of the hepatic lobules occurred during operation in a large number of cases. Correlation of this change with possible factors at operation, such as hepatic trauma by retractors, operating time, amount of anesthetic agent, intravenous administration of fluids and decrease in blood pressure, produced evidence of a consistent relationship between such infiltration and trauma and a less extensive relationship between this change and the intravenous administration of fluids. The other factors at operation apparently had no effect on this infiltration.

Correlation of polymorphonuclear infiltration of the liver with the presence of systemic infection, hepatic periportal inflammation, disease of the gallbladder, abnormal results of studies of hepatic function, and the age and sex of the patients demonstrated no apparent relationship with any one factor, except for a slight increase in the incidence of such infiltration in women and in patients of older age groups.

It is considered that such infiltration is of no clinical importance and that it must be regarded as a traumatic artifact occurring in material taken during surgical biopsy.

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OBSERVATIONS ON THE POSTOPERATIVE CIRCULATION

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OPERATIVE measures in any form are associated with stress on the circulatory apparatus of the organism. This stress may, if pronounced, lead to central or peripheral circulatory insufficiency or a combination of both. The occurrence of this insufficiency is dependent on several factors, including the preoperative condition (arteriocardiosclerosis, neoplasms, decreased blood volume, hypoproteinemia, and anemia). The degree of circulatory insufficiency may vary from that which is scarcely detectable clinically to manifest shock. In 1941, Harild reviewed earlier investigations on the postoperative circulation and pointed out that their results were very inconsistent, owing to, among other things, the absence of suitable methods of examination for use in human beings. In his own investigations Harild was mainly concerned with determinations of the cardiac output and its variations following different types of operations. He employed Grollman's acetylene method and determined the cardiac output daily in a series of 26 patients. In 15 of them he found a decreased cardiac output concomitantly with increased oxygen consumption.

Cournand, Riley, Bradley, Breed, Noble, Lauson, Gregerson, and Richards (2) used the heart catheterization technique in studying the circulation in the presence of various forms of shock. They investigated 36 cases and found a decrease of 30 to 50 per cent in the cardiac output in patients with moderately severe to very severe shock.

Sjöstrand (8, 9) has called attention, in a number of papers, to the significance of the pulmonary blood volume as a regulator of the blood circulation in normal and pathologic conditions.

Johnson studied the effect of various anesthetics upon the circulation in man, with special reference to the significance of the pulmonary blood reservoir.

Troell, using the technique reported by Cournand and Ranges (1), studied the circulation during the first day after operation in 23 patients. He found a postoperative increase of the cardiac output that was statistically significant in a group of 7 cases.

The literature contains only a few reports on investigations into the postoperative hemodynamics with the use of those facilities that heart catheterization affords. We therefore, believed that it would be worth while to continue the studies earlier embarked upon by Troell.

The purpose of these investigations was to study the circulation following extensive abdominal operations in patients treated preoperatively and postoperatively according to the principles currently applied at the Department of Surgery, Karolinska Sjukhuset.

METHOD

The investigations were conducted on patients who were to undergo relatively extensive abdominal operations. In each case the heart was examined prior to operation. All patients were submitted to electrocardiographic examinations comprising standard limb leads and 5 chest leads. The majority were subjected to hypoxemia test or work test on a bicycle ergometer. The customary preparatory measures were taken, i.e., no food or drink for 12 hours before operation. Premedication with morphine and scopolamine, according to age, was given 1½ hours before the start of the examination, which usually commenced at 8:00 a.m. The heart catheter was inserted into a vein of the arm and advanced, under fluoroscopic control, to one of the main branches of the pulmonary artery, then sutured in the skin. During this procedure the patients were under light general anesthesia, produced by small amounts of narkotal® (isopropyl-β-bromallyl-N-methyl-malonyl-carbamide sodi-

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um), administered intravenously, the dose averaging about 10 milliliters. The purpose of this light anesthesia was to spare the patients from the further mental stress attending insertion of the catheter, and in this way we sought to obtain some measure of uniformity and comparableness in the initial condition before operation. When the position of the catheter had been checked, the patients were allowed to recover consciousness, and not until then were the blood samples taken. The oxygen consumption was determined with a Douglas' bag. At the same time, blood samples were taken from the pulmonary artery and a peripheral artery. These were analyzed with respect to the content of oxygen and carbon dioxide and the oxygen capacity by the method of van Slyke, with double determinations of each sample. The cardiac output was calculated by using Fick's direct method. Recording of the pulmonary arterial pressure was done with the method reported by Tybjaerg Hansen. The peripheral arterial pressure was determined by the auscultatory method, and the pulse rate was recorded.

After completion of the preoperative tests, which usually required 1 to 2½ hours, the operations were carried out. The catheter was kept in the pulmonary artery throughout the day of examination. As a rule, further samples were taken 3 times (2 to 4, 5 to 9, and 18 to 24 hours after operation). They could not be taken at definite intervals because the postoperative condition of the patients did not always enable them to co-operate in determination of the oxygen consumption, we accordingly waited until they were fully awake and relaxed. To prevent coagulation in the catheter, the latter was connected to a heparin drip consisting of 0.050 gram of heparin per 1,000 milliliters of 5.5 per cent glucose. Occasionally, coagulation in the catheter made it impossible to carry out more than 1 or 2 postoperative determinations. Whenever a fresh sample was taken the position of the catheter was checked by studying the pressure curves. In some cases the position was adjusted under fluoroscopic control. During and after the operations the patients received conventional substitution therapy; i.e., blood losses were compensated with blood, and in addition 2,000 milliliters of fluid were administered parenterally during the first day. In no case were any complications observed which could be attributed to the catheterization or to retention of the heart catheter for about 24 hours.

MATERIAL

Twenty-one patients—20 males and 1 female—were studied. Nineteen were referable to Gordh's risk groups I and II[1] and 2 to risk group III. Thirteen patients, or more than one-half, underwent operations for gastric or duodenal ulcer. Three underwent subtotal colectomy, 3 cholecystectomy, and 2 resection of the vagus for peptic ulcer. The series includes no cancer case.

In the first 24 hours of the postoperative course there was complete freedom from complications clinically in 16 cases. Three patients (Cases 3, 6, and 20) showed signs of slight affection in the form of sweats and some restlessness; 2 (Cases 17 and 19) were severely affected, presenting signs of shock.

Two patients (Cases 1 and 14) died, 1 of peritonitis and uremia on the fourth day after operation and the other of pancreatitis and uremia on the tenth day. Both of these cases were clinically free of complications during the first 24 hours.

RESULTS

A comparison of the values obtained in the 5 postoperatively affected cases and the corresponding values in the 16 cases that were not affected shows no statistically significant differences. The results presented in the following are, therefore, based on the entire series and will be found in Tables I to X and Figures 1 to 4.

KEY TO THE TABLES AND FIGURES

The mean, standard deviation and standard error of the mean have been computed according to the conventional statistical meth-

[1]Risk I denotes that the patient showed no organic disease, or that the pathologic process which was to be surgically treated was localized and had not given rise to any systemic disturbances.

Risk II denotes a moderate but demonstrable systemic disturbance due either to the condition that was to be surgically treated or to some other operative complication.

Risk III denotes severe systemic disturbance, whatever the cause or causes.

Risk IV denotes extreme systemic disorders.

TABLE I.—OXYGEN CONSUMPTION BEFORE AND AFTER OPERATION

Oxygen consumption, ml./min.		$\bar{d} \pm \epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x} \pm \epsilon_{\bar{x}}$ σ_x				
I	154 ± 9.3 41.5				
		II—I +65.2±13.2	4.9	<0.001 (20)	S***
II	213.9±13.4 61.4				
		III—I +64.3±19.0	3.4	0.014 (7)	S*
III	214.9±23.4 66.0				
		IV—I +71.2±10.7	6.7	<0.001 (18)	S***
IV	232.6±14.1 61.4				

The consumption is significantly increased postoperatively.

ods described by Fisher. The means of differences are computed from the individual differences between postoperative and preoperative values. The differences are approximately normally distributed. The following symbols are used:

x = variable
n = number of observations
$\bar{x}$ = mean of observations
σx = standard deviation
$\epsilon_{\bar{x}}$ = standard error of the mean
d = differences between variables
$\bar{d}$ = mean of differences
$\epsilon_{\bar{d}}$ = standard error of the mean of differences
t = t value
P = probability
NS = not significant ($P > 0.05$)
S* = probably significant ($0.05 \geqq P > 0.01$)
S** = significant ($0.01 \geqq P > 0.001$)
S*** = very significant ($P \leqq 0.001$)
I = preoperative observation
II = observations made 2 to 4 hours after operation
III = observations made 5 to 9 hours after operation
IV = observations made 18 to 24 hours after operation

In Figures 1 to 4 will be found the mean curves showing the course of the factors studied. Tables I to X show the mean values, standard errors, distribution, means of differences and their significance.

The following observations were made:

1. The oxygen consumption rose postoperatively. The increase was especially pronounced after 18 to 24 hours (Table I and Fig. 1).

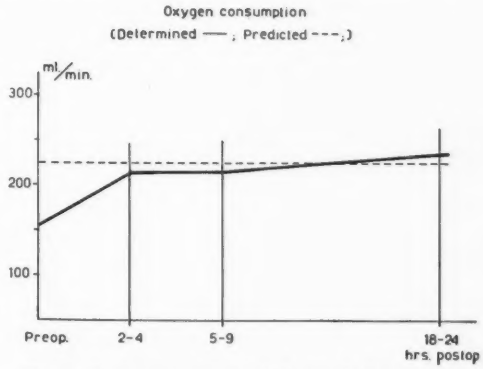

Fig. 1. Oxygen consumption before and after operation. Predicted in relation to observed values.

2. The venous oxygen content fell significantly after 18 to 24 hours.

3. The arterial oxygen content showed a postoperative fall that was especially pronounced after 5 to 9 and 18 to 24 hours.

4. The oxygen capacity after operation showed no conspicuous divergences from the preoperative value.

5. The arterial oxygen saturation showed a demonstrable fall after 5 to 9 and 18 to 24 hours. The decrease averaged about 5 to 6 per cent of the preoperative value (Table II and Fig. 2).

6. The venous oxygen saturation was increased after 2 to 4 hours but decreased after 18 to 24 hours. The fall amounted to about 8 to 9 per cent of the preoperative value.

7. The venous carbon dioxide content was markedly decreased 2 to 4 hours postoperatively, after which it showed an increase, but without reaching the preoperative value (Table III and Fig. 2).

8. The arterial carbon dioxide content showed the same course as the venous (Table IV and Fig. 2).

9. The difference between the arterial and the venous oxygen content was decreased after 2 to 4 and 5 to 9 hours but increased after 18 to 24 hours. Only the difference after 2 to 4 hours was statistically significant (Table V and Fig. 3).

10. The cardiac output showed a substantial rise postoperatively. The increase amounted to about 30 to 50 per cent and was specially

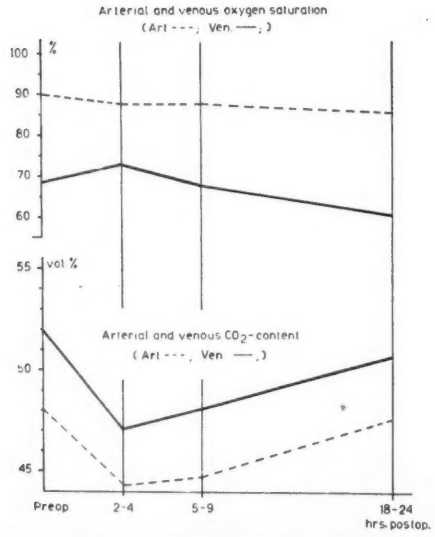

Fig. 2. Heart rate, arteriovenous oxygen difference and cardiac output before and after operation.

pronounced during the first 5 to 9 hours (Table VI and Fig. 3).

11. The mean pressure in the pulmonary artery was not significantly changed (Table VII).

12. The systolic and the diastolic blood pressure showed a slight increase after 18 to 24 hours (Tables VIII and IX).

13. The heart rate showed a rise that was statistically significant during the first 18 to 24 hours (Table X and Fig. 3).

TABLE III.—VENOUS CARBON DIOXIDE CONTENT BEFORE AND AFTER OPERATION

Venous CO_2 content, vol. per cent		$\bar{d}\pm\epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x}\pm\epsilon_{\bar{x}}$ σ_x				
I	52.09±0.64 2.8	II—I −4.35±0.61	7.2	<0.001 (20)	S***
II	47.75±0.58 2.5	III—I −3.26±1.16	2.8	0.032 (7)	S*
III	48.25±1.32 3.4	IV—I −0.66±0.86	0.8	0.43 (18)	NS
IV	51.08±0.79 3.3				

The content is decreased postoperatively, most significantly after 2 to 4 hours.

DISCUSSION

The most pronounced changes that were found postoperatively in the present investigation consisted in the increased oxygen consumption, cardiac output and heart rate, and the decreased arterial and venous oxygen saturation as well as the fall in the arterial carbon dioxide content and the venous carbon dioxide content.

The preoperative oxygen consumption values were about 30 per cent lower than the corresponding predicted standard values. This discrepancy was probably due to the effect of morphine and scopolamine and to the light narkotal anesthesia which had been given shortly before. Johnson (1951) found a fall of 10 to 30 per cent in the oxygen consumption during narkotal anesthesia in 6 cases.

TABLE II.—ARTERIAL OXYGENATION BEFORE AND AFTER OPERATION

Arterial oxygenation, per cent		$\bar{d}\pm\epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x}\pm\epsilon_{\bar{x}}$ σ_x				
I	90.23±0.62 2.8	II—I −1.52±0.84	1.8	0.09 (17)	NS
II	88.78±0.86 3.5	III—I −4.66±1.66	2.8	0.048 (5)	S*
III	87.08±0.67 1.4	IV—I −5.04±1.28	3.9	0.002 (14)	S**
IV	85.41±1.33 4.9				

A significant decrease is demonstrable after operation.

TABLE IV.—ARTERIAL CARBON DIOXIDE CONTENT BEFORE AND AFTER OPERATION

Arterial CO_2 content, vol. per cent		$\bar{d}\pm\epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x}\pm\epsilon_{\bar{x}}$ σ_x				
I	48.56±0.64 2.8	II—I −4.19±0.83	5.0	0.001 (20)	S***
II	44.37±0.63 2.8	III—I −3.08±1.20	2.6	0.040 (7)	S*
III	44.79±1.36 3.6	IV—I −0.43±0.57	0.8	0.43 (18)	NS
IV	47.85±0.84 3.5				

The content decreased postoperatively, significantly after 2 to 4 hours.

TABLE V.—DIFFERENCE IN ARTERIAL AND VENOUS OXYGEN CONTENT BEFORE AND AFTER OPERATION

Difference in arterial and venous oxygen content, ml./l.		$\bar{d}\pm\epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x}\pm\epsilon_{\bar{x}}$ σ_x				
I	40.2±2.6 11.7				
II	32.7±2.8 12.3	II—I −7.6±3.1	2.5	0.022 (14)	S*
III	36.2±4.5 12.0	III—I −5.6±5.5	1.0	0.36 (6)	NS
IV	46.6±2.7 11.7	IV—I +5.4±3.4	1.6	0.15 (19)	NS

The difference is decreased 2 to 4 hours postoperatively and increased after 18 to 24 hours.

The oxygen consumption, determined 2 to 4 hours after operation, showed an increase of 40 per cent on the preoperative values. The anesthetic given during the operation, which in each case was narkotal in combination with a relaxant, has in itself a depressing effect on the oxygen consumption. Moreover, the operative anesthesia was considerably longer and deeper than that produced for insertion of the catheter. Nevertheless, the oxygen consumption still showed a marked rise.

At the subsequent postoperative determinations of the oxygen consumption, the latter showed values approximating to the predicted standard values (Fig. 1). Harild found a rise of 40 per cent in the oxygen consumption postoperatively in a group of laparotomy cases; Troell, an increase of 10 to 15 per cent in risks I and II and of 50 per cent in risk III.

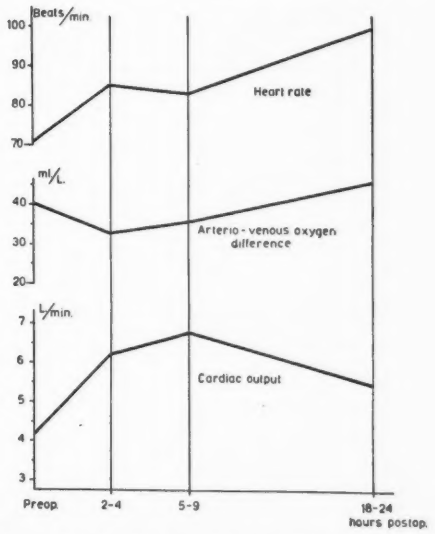

Fig. 3. Arterial and venous oxygen saturation and carbon dioxide content before and after operation.

The cardiac output rose by 30 to 50 per cent. The oxygen consumption had increased, and the difference between the arterial and venous oxygen content had decreased by about 20 per cent, on determination 2 to 4 hours after operation. At the later observations the oxygen consumption was more or less unchanged and the difference in the arterial and the venous oxygen content had risen (Fig. 2).

TABLE VI.—CARDIAC OUTPUT BEFORE AND AFTER OPERATION

Cardiac output, l./min.		$\bar{d}\pm\epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x}\pm\epsilon_{\bar{x}}$ σ_x				
I	4.15±0.32 1.45				
II	6.11±0.44 1.8	II—I +1.99±0.42	4.7	<0.001 (18)	S***
III	6.40±1.09 2.8	III—I +1.99±0.76	2.6	0.036 (7)	S*
IV	5.33±0.40 1.7	IV—I +1.22±0.44	2.8	0.012 (19)	S*

The output is significantly increased postoperatively.

TABLE VII.—MEAN PRESSURE IN THE PULMONARY ARTERY

Mean pressure, pulmonary artery, mm. Hg		$\bar{d}\pm\epsilon_{\bar{d}}$	t	P (n)	Significance
Time of observation	$\bar{x}\pm\epsilon_{\bar{x}}$ σ_x				
I	16.2±1.2 5.5				
II	14.5±1.6 6.7	II—I −2.2±2.3	0.9	0.38 (19)	NS
III	14.9±3.23 8.5	III—I −0.3±3.7	0.1	0.92 (7)	NS
IV	16.1±1.9 7.2	IV—I 1.0±2.4	0.4	0.70 (15)	NS

No significant variations can be demonstrated.

TABLE VIII.—SYSTOLIC BLOOD PRESSURE BEFORE AND AFTER OPERATION

Systolic blood pressure, mm. Hg					
Time of observation	$\bar{x} \pm \epsilon_{\bar{x}}$ σ_x	$\bar{d} \pm \epsilon_{\bar{d}}$	t	P (n)	Significance
I	121±3.1 14.2	II—I +2.2±4.2	0.5	0.62 (18)	NS
II	121±4.4 18.6	III—I +2.0±4.6	0.4	0.71 (5)	NS
III	132±11.1 24.9	IV—I +10.8±4.4	2.5	0.022 (20)	S*
IV	133±5.3 23.5				

A slight increase is demonstrable after 18 to 24 hours.

TABLE IX.—DIASTOLIC BLOOD PRESSURE BEFORE AND AFTER OPERATION

Diastolic blood pressure, mm. Hg					
Time of observation	$\bar{x} \pm \epsilon_{\bar{x}}$ σ_x	$\bar{d} \pm \epsilon_{\bar{d}}$	t	P (n)	Significance
I	80±5.7 5.6	II—I −3.9±3.3	1.2	0.25 (18)	NS
II	77±3.7 15.8	III—I +13.0±10.8	1.2	0.29 (5)	NS
III	91±15.3 34.1	IV—I +7.3±2.6	2.8	0.012 (20)	S*
IV	87±3.1 13.7				

A slight increase can be demonstrated after 18 to 24 hours.

Troell found an increase of 30 to 50 per cent in the cardiac output postoperatively; but Harild, on the other hand, observed a decrease in 15 cases of 26. Harild's results were based, however, on observations made 24 hours at the earliest after operation, and moreover he used a different method. A direct comparison of Harild's results on the one hand, and Troell's and ours on the other, is scarcely feasible.

The heart rate showed a continuous rise throughout the course of examination. This is of major importance to the understanding of the postoperative circulation. An increased heart rate coinciding with an unchanged cardiac output connotes a fall in the stroke volume. A reduced stroke volume is present, for instance, as indicated by Cournand and associates, in decreased blood volume, or in inadequate distribution of the blood volume, with consequent emptying of the pulmonary blood reservoir as Sjöstrand has shown (Fig. 2). A low stroke volume and high heart rate might be attended by a fall in the mean blood flow through the coronary vessels. It may, in cases with relative coronary insufficiency, be associated with myocardial anoxia, resulting in myocardial insufficiency. This may conceivably be the mechanism of origin in the postoperative cardiac circulatory insufficiency sometimes observed in elderly and arteriosclerotic patients.

In the present series a decrease of 5 per cent in the arterial and venous oxygen saturation was obtained. Corresponding values have been reported by Troell. Concomitantly with the reduced oxygen saturation, a marked fall was observed in the arterial and venous carbon dioxide content—an observation that we have not been able to find in the available literature (Fig. 3).

The reduced oxygen saturation and carbon dioxide content postoperatively may be attributable to the occurrence of *ineffective alveolar ventilation*. Diaphragmatic fixation due to pain, together with the presence of atelectasis and accumulation of secretion in the lungs, modify the requisites for interchange of gases between alveoli and blood. The blood from the right heart will not be completely oxygenated if a portion of the lung is poorly ventilated and if it is totally unventilated, a true venoarterial shunt will be established. The result will be decreased oxygen saturation. This, via excitation of the chemoreceptors, produces hyperventila-

TABLE X.—HEART RATE BEFORE AND AFTER OPERATION

Heart rate, beats/min.					
Time of observation	$\bar{x} \pm \epsilon_{\bar{x}}$ σ_x	$\bar{d} \pm \epsilon_{\bar{d}}$	t	P (n)	Significance
I	71.1±2.4 10.7	II—I +13.2±3.8	3.5	0.002 (20)	S**
II	85.2±3.5 15.4	III—I +13.9±4.5	3.1	0.014 (9)	S*
III	83.6±4.2 12.5	IV—I +25.9±3.8	6.8	<0.001 (18)	S***
IV	97.4±3.4 14.6				

The rate is significantly increased postoperatively.

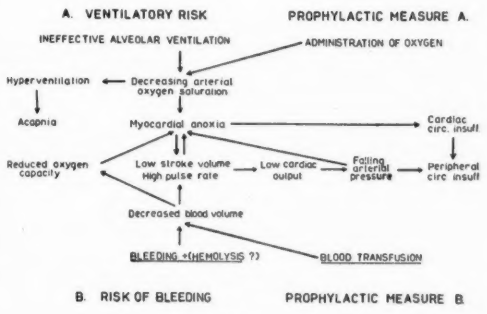

Fig. 4.

tion, leading to acapnia. The hyperventilation, however, in the event of venoarterial lung shunting, will not suffice to give satisfactory oxygen saturation of the arterial blood, the patients accordingly developing a condition of anoxia and acapnia postoperatively. However, the observed reduction of the carbon dioxide content of both arterial and venous blood is somewhat obscure in nature, and the aforementioned hypothesis will be the subject of further investigations.

The observations made in the present investigation—namely, that during the first 24 hours after operation, (1) the oxygen consumption increases, (2) the cardiac output rises, (3) an arterial anoxia appears, and (4) arterial and venous acapnia may develop—should warrant the following therapeutic considerations and measures.

Postoperative administration of oxygen should be of value. In this way it is possible to avoid or reduce the postoperative anoxia except in the presence of a venoarterial shunt.

Any tendency to reduction of the blood volume must be combatted. Blood losses should be compensated as soon as possible—if practicable, during the operation itself. An unfavorable distribution of the blood volume can be corrected by ensuring an adequate position of the patient, with the head lowered, of course provided that no special contraindications are present.

The two chief postoperative risk factors—bleeding and inadequate ventilation—may, either alone or in combination, give rise to cardiac and/or peripheral circulatory insufficiency. The relationship is schematically shown in Figure 4.

SUMMARY

1. Twenty-one patients were examined, before and during the first 24 hours after extensive abdominal operations, with respect to cardiac output, pressure in the pulmonary and systemic circulation, and blood gases.

2. The cardiac output increased by 30 to 50 per cent after operation.

3. The arterial oxygen saturation fell by about 5 per cent.

4. The carbon dioxide content of both arterial and venous blood fell postoperatively.

5. Measures to prevent or to remedy such postoperative complications are discussed.

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CARCINOMA OF THE COLON AND RECTUM

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THE examination and treatment of 252 cases of carcinoma of the colon or rectum seen at the George F. Geisinger Memorial Hospital and Foss Clinic during the 5 year period 1946 through 1950 form the basis of the present study.

A follow-up was obtained on all 252 patients; they were followed through the tumor clinic and examined periodically at 6 month intervals. All surviving patients were examined by members of the surgical staff of the George F. Geisinger Memorial Hospital and Foss Clinic between March 1, 1953, and June 1, 1953, or were examined by their own physicians, and reports were sent to the tumor clinic.

AGE AND SEX INCIDENCE

The average age of the patients in this series was 60.92 years, the oldest being 85 and the youngest 20 years old. As can be seen from Table I, the majority of the cases (76.98 per cent) occurred in the sixth, seventh, and eighth decades. There were 136 males and 116 females. No significant correlation has been found between age and survival. Old age itself, however, is not a contraindication to resection for carcinoma of the colon or rectum.

SYMPTOMS AND SIGNS

The following percentages cover the major diagnostic findings: weight loss (76.28 per cent), pain (69.96 per cent), palpable mass (68.25 per cent), melena (66.40 per cent), weakness (62.03 per cent), constipation (57.31 per cent), and diarrhea (40.71 per cent). All the symptoms and signs are listed in order of frequency in Table II.

Pain varied from mild to severe and was variously described as "crampy" or "griping" in character and usually was initiated by eating or was coincident with the desire for, or act of, defecation.

Rectal bleeding occurred usually at the time of defecation in lesions of the left side of the colon. Anemia was not seen as frequently with lesions of the left side of the colon as with lesions of the right side, yet rectal bleeding was only rarely noted in right colon lesions.

The average amount of weight loss was 20.33 pounds.

A mass could be palpated in 172, or 68.2 per cent, of the patients. Rectal palpation revealed 104 lesions. Masses were palpable abdominally in 65 patients. In 3 patients a mass was palpable both rectally and abdominally.

DURATION OF SYMPTOMS

A universally accepted explanation for failure of treatment in carcinoma of the colon or rectum is delay in recognition of the disease even after definite symptoms present themselves. In this series there was a 7.18 month delay after the occurrence of symptoms before the diagnosis was made. Since this delay was figured conservatively, the actual delay was no doubt greater. The responsibility for delay in diagnosis rests with the patient in the majority of instances. However, we did find a delay of 4.82 months between diagnosis and operation, which, apparently, had to be shared equally between the family physician and the patient.

This delay in providing treatment occurred in 16.6 per cent of the series. With 3 patients there were delays of 12, 10, and 6 months respectively, due, we thought, to negligence of the physician. All these patients had inoperable lesions when they finally came to the hospital. Combined negligence of patient and physician led to a 17 month delay and inoperability with another patient. A delay of 8 months, due to the patient's own procrastination, also added to the number of inoperable cases.

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It has been our impression that rural patients are seen at a later time than those in metropolitan clinics. This fact has been borne out by comparison of the above statistics with those of Ransom and Portmann.

Four of these patients exhibited a curious resistance to carcinoma, a factor emphasized in the recent article of Morton and Morton. Despite a delay of some 24 months, 1 patient was found to have no metastases at the time of exploration. Delay of 21, 12, and 23 months respectively did not lead to inoperability in the other 3 patients.

A widely accepted explanation of delay in diagnosis is inadequate examination by the family physician. In this series we found 75 patients, or 29.76 per cent, in whom the diagnosis was missed by the physician for a number of months, presumably because of inadequate examination (Table III).

With the majority of these patients no diagnosis was made or the patient was treated for hemorrhoids or some other condition, the carcinoma being undetected. Many others had been treated for anemia or constipation for long periods of time.

There were, unfortunately, 9 patients in this series in whom the diagnosis of carcinoma was missed for varying periods of time by physicians of considerable skill. Two patients were treated for anemia, by well trained internists, for periods of 16 and 27 months without barium studies being made. Carcinoma was later found in both. Not all of these conditions can be recognized even with complete studies, as is attested by the fact that there were 2 patients who had repeated negative barium enemas before the carcinoma was isolated. One patient had a vaginal hysterectomy 3 months before carcinoma of the rectum was found; 1 patient had a cholecystectomy 1 month before a carcinoma of the transverse colon was discovered; and 1 patient was operated upon for a strangulated inguinal hernia 5 months before a diagnosis of carcinoma of the cecum was made. With this patient the carcinoma was obscured by other and more prominent diseases. One patient had chronic pyelitis and diabetes, and the carcinoma of the sigmoid was not recognized for 4 months, because of the more striking symptoms of the other diseases. The symptoms of still another patient were attributed entirely to diabetes mellitus before a carcinoma of the descending colon was discovered.

TABLE I.—AGE INCIDENCE

Age, years	Total No.	Per cent
20-29	3	1.19
30-39	7	2.78
40-49	33	13.09
50-59	68	26.98
60-69	79	31.35
70-79	47	18.65
80-89	15	5.96

X-RAY EXAMINATIONS

In 130 patients, or 51.38 per cent, of those in this series the diagnosis was made by x-ray examination. In 16 patients, 10.96 per cent of those examined roentgenographically, the diagnosis was not made or even suspected, yet a carcinoma was present. We note that there is a definite fallibility in x-ray diagnosis, as has been mentioned by Finney and Stone. It should be emphasized that lesions of the rectum and lower sigmoid usually cannot be so readily recognized by x-ray examination, yet they are usually palpable on rectal examination or visible on proctoscopic examination.

LOCATION

The majority of the lesions were found in the rectum, rectosigmoid, and sigmoid regions, the incidence being 68.49 per cent. Table IV and Figure 1 show the number and percentage of carcinomas found in the different locations in the colon and rectum.

Among all the lesions there were 10 carcinomatous polyps of the rectum or rectosigmoid. Seven of the 10 patients are still living, 4 having had multiple excisions and fulgura-

TABLE II.—SYMPTOMS AND SIGNS

	No.	Per cent
Weight loss	193	76.28
Pain	177	69.96
Palpable mass	172	68.25
Melena	168	66.40
Weakness	157	62.03
Constipation	145	57.31
Diarrhea	103	40.71
Alternating diarrhea and constipation	70	27.66
Vomiting	48	18.97
Mucus in stool	35	13.43
Obstruction	26	10.27
Anemia	11	4.35

TABLE III.—MISSED DIAGNOSIS

	No. cases
Hemorrhoids or hemorrhoidectomy	16
No diagnosis (M.D. visits)	16
Anemia	10
Constipation	8
Diarrhea	3
Fulgurated polyp	3
Appendectomy	2
Barium enema negative	2
Gallbladder disease	2
Abdominal hysterectomy	2
Vaginal hysterectomy	1
Strangulated hernia	1
Appendiceal abscess	1
Diverticulosis	1
Colitis	1
Rectal abscesses	1
Salpingitis	1
Prostatic hypertrophy	1
Chronic pyelitis and diabetes	1
Diabetes	1
Neuralgia	1

tions of the growths. Of the 3 patients who died, 1 patient did not return following excision; 1 was inoperable at the time of examination because of advanced age; and the other patient was 77 years of age when he had the first of multiple excisions and fulgurations.

OPERABILITY

Of the 252 patients, 137, or 55.24 per cent, had operable lesions. An additional 20 patients had conditions considered possibly operable; 6 of these patients survived 4½ years, 4 others survived 2½ years, and the other 10 patients had only short survivals. Ninety-one patients had inoperable lesions, and 4 others refused surgery.

Of the inoperable patients, 1 whose carcinoma of the colon also involved the left kidney and the pancreas survived 29 months. Only 1 other patient in this group lived longer. At laparotomy this patient's carcinoma was found to involve the posterior abdominal wall and 1 iliac artery, and no resection was possible, yet he survived 4½ years.

Twenty-two patients, or 8.73 per cent, had intestinal obstruction on admission. In this group 19 cecostomies, 2 loop colostomies, and 1 ileostomy were performed prior to definitive surgery.

TABLE IV.—LOCATIONS OF CARCINOMA OF THE COLON AND RECTUM

Site	Total No.	Per cent
Cecum	25	9.84
Ascending colon	14	5.51
Hepatic flexure	5	1.97
Transverse colon	13	5.12
Splenic flexure	7	2.78
Descending colon	14	5.51
Sigmoid	43	16.53
Rectosigmoid	30	11.80
Rectum	102	40.16
Anus	1	0.39
Colon (origin undetermined)	1	0.39

There were 2 double carcinomas, 1 patient had both the rectum and anus involved and the other patient had both the cecum and the transverse colon involved.

SURGICAL TREATMENT

Preoperatively, our patients are admitted at least 5 days before operation. In addition to having a thorough physical examination, they are placed on the usual high protein, nonresidue diet and nightly enemas are also given. At least 1 blood transfusion is given to help correct the anemia which is usually present. It is our practice to administer sulfasuxidine for 5 days prior to operation. This was carried out in 195, or 90.28 per cent, of the 216 patients operated upon in the present series.

There were 59 one stage abdominoperineal resections of the Miles type; 37 anterior resections of the rectosigmoid and sigmoid; 29 resections of the transverse and descending colon; 24 hemicolectomies; 43 exploratory laparotomies; 10 fulgurations; and 14 other operations, consisting of 2 palliative sigmoid resections with colostomy, 3 cecostomies, 1 colotomy, 2 Mikulicz resections, 1 first stage abdominoperineal resection, 1 cecum resection, and 4 two stage abdominoperineal resections.

There were 2 one stage abdominoperineal resections which included a total hysterectomy, and 2 others which included a partial resection of the bladder. One Miles resection also included resection of a metastatic liver nodule, and another included a bilateral salpingo-oophorectomy. One patient refused operation for 2 years before she finally returned and agreed to an abdominoperineal resection. Interestingly enough, there was no evidence of metastasis at operation. The patient is still alive 3 years after the carcinoma was first discovered.

Partial bladder resections were also carried out in 2 anterior resections of the rectosig-

moid and sigmoid. Another anterior sigmoid resection included a bilateral salpingo-oophorectomy. In 1 anterior resection of the sigmoid it was also necessary to resect the cecum because of local extension of the carcinoma.

Involvement of the stomach in 1 case necessitated partial gastric resection together with resection of the transverse colon. With 1 patient who had a carcinoma of the cecum and of the transverse colon, a right hemicolectomy included resection of all the transverse colon. A portion of the anterior abdominal wall had to be resected in another hemicolectomy. There were 2 palliative sigmoid resections establishing a colostomy and leaving the rectum, and 3 cases in which cecostomy was the only surgical procedure. One of the 3 cecostomy patients refused further surgery and the other 2 died before their condition was satisfactory for definitive surgery. One patient had only the cecum resected, a complete hemicolectomy not being carried out because of gross contamination of the peritoneum from a pericecal abscess.

All of the anastomoses were carried out by the open technique, as now frequently advocated. Diversion of the fecal stream by proximal colostomy or cecostomy was not resorted to except in cases of obstruction.

In patients with advanced lesions or with liver metastases, we doubt whether colostomy is as beneficial as many believe. We wholeheartedly agree with Lahey and others that liver metastasis, infiltration of the bladder, or lateral fixation in rectal carcinoma makes radical resection frequently inadvisable.

SURVIVAL

Since this study included the years 1946 through 1950, the 5 year survival information of all the patients will not be available until after January 1, 1956. This report was concluded on June 1, 1953, yet some evaluation of the 5 year results can be made covering some of the patients studied.

There were 120 consecutive patients with carcinoma of the colon or rectum who were seen between January 1, 1946 and June 1, 1948 all of whom could be studied for 5 year survival data. Twenty-two of these patients had inoperable lesions, 1 refused operation, 26 had only exploratory laparotomies, while 1 had a palliative operation, leaving 70 patients who had definitive surgical treatment. Thirty patients, or 42.86 per cent, having definitive surgery, survived 5 years or more. One of these patients has since died of carcinoma, but all the others are still alive and without recurrence. Twenty-five per cent of the entire group of 120 consecutive patients with carcinoma survived 5 years.

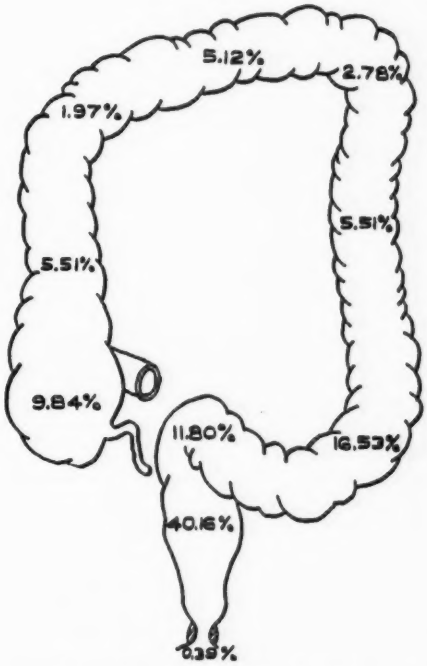

Fig. 1. Location carcinoma of colon.

Figure 2 and Table V show the length of survival of the patients who have succumbed to carcinoma. The majority died within the first 12 months—43.68 per cent within 6 months, 20.11 per cent in 6 to 12 months, and 20.11 per cent in 12 to 24 months. After the first 2 years, the mortality rate leveled off rapidly.

There were 5 deaths in the series not caused by carcinoma: 2 due to myocardial infarction, 1 from pulmonary edema and paralytic ileus, 1 from uremia and heart failure, and 1 from myocardial infarction secondary to a mesen-

TABLE V.—DEATHS IN RELATION TO SURVIVAL

Time, months	1946	1947	1948	1949	1950	Total	Per cent
0- 6	18	18	16	13	11	76	43.68
6-12	4	7	8	8	8	35	20.11
12-24	7	4	7	6	11	35	20.11
24-36	1	3	2	8	2	16	9.20
36-48	3	3	1	2	-	9	5.17
48-60	0	1	2	-	-	3	1.72
Total	33	36	36	37	32	174	

teric thrombosis. The cause of death was determined by autopsy, no carcinoma being found. These cases are included in Table V.

A tabulation of the patients still surviving indicates a survival period of: 1 to 1½ years in 1 case, 2 to 2½ years in 5 cases, 2½ to 3 years in 5 cases, 3 to 3½ years in 6 cases, 3½ to 4 years in 6 cases, 4 to 4½ years in 11 cases, 4½ to 5 years in 12 cases, over 5 years in 29 cases. The 3 patients who refused operation have not been included in these tabulations. However, the 1 patient who had a preliminary cecostomy and then refused further operation is included.

COMPLICATIONS

Detailed reports of complications following colonic surgery have been made by Binkley and Deddish as well as some others who have studied the subject.

TABLE VI.—POSTOPERATIVE COMPLICATIONS

	No. cases
Urinary retention, cystitis, "neurogenic bladder"	28
Perineal urinary fistula	3
Uremia	1
Wound dehiscence	5
Wound abscess	8
Fecal fistula	7
Peritonitis	7
Mesenteric thrombosis	1
Intestinal obstruction	2
Gastrointestinal hemorrhage	2
Gangrene of colostomy	1
Pulmonary embolus	5
Phlebothrombosis	1
Thrombophlebitis	1
Congestive failure	4
Auricular fibrillation	3
Myocardial infarct	2
Pneumonia	2
Pleurisy	1
Atelectasis and chronic bronchitis	1
Acute tubotympanitis	1
Epileptic seizure and penicillin dermatitis	1
Total	87

It is proposed here to report our complications and to analyze them. Sixty-eight of the 216 patients operated upon had 1 or more postoperative complications. Thus, 31.48 per cent of patients operated upon suffered complications with varying degrees of severity. Fourteen of these patients had more than 1 complication.

About half of the complications occurred with patients having a one stage abdominoperineal resection. With 28 patients, or 41.18 per cent, the complication was urinary retention with cystitis. Three patients, or 4.56 per cent, had a temporary perineal urinary fistula (Table VI).

It is interesting to note that despite the large proportion of patients developing urinary retention and the so-called neurogenic bladder, the actual cause for this complication is none too clear. The factors of trauma and interference with nerve control, especially injury to the pudendal nerves, have been suggested as the cause, the subject having been extensively studied by Marshall, Pollack, and Miller. Some of these conditions are due to bladder-neck obstruction caused by prostatic hypertrophy, and can be relieved by transurethral resection, but there is still a certain percentage in which the condition persists even after an adequate prostatectomy. These authors suggest the theory of loss of bladder and bladder-neck support as the cause of the complication, and they offer as evidence several case reports showing correction after suprapubic bladder suspension.

Of the 28 cases of urinary retention in this series, all but 9 cleared up on conservative management. The others disappeared following transurethral prostatectomy.

Despite careful closure of the fascia with interrupted No. 000 cotton sutures and the use of retention sutures, there were 5 cases of wound dehiscence. This complication is not uncommon in debilitated patients with cancer. We do not believe that the use of other suture material, stainless steel wire, for example, as advocated by some authors can prevent it.

We agree with Garlock, Ginzburg, and Glass that perforation of the colon from car-

cinoma frequently proves fatal. There were 8 cases of peritonitis with 6 deaths after operation. Three deaths resulted from spontaneous perforation of the colon following exploration alone, while 2 deaths resulted from leakage at the anastomosis. One other patient had a perforation of the ileum secondary to mesenteric thrombosis.

Despite careful routine preoperative preparation with sulfasuxidine, there were 7 cases of postoperative fecal fistula and 8 wound infections. Five of the fecal fistulas healed spontaneously, yet it was necessary to excise 1 and establish a proximal loop colostomy in another before the sinus closed.

It is apparent that, despite attempted preoperative sterilization of the bowel and the use of postoperative antibiotics, attention must still be paid to a most careful technique in the anastomosis. There were 2 instances of postoperative intestinal obstruction, 1 requiring lysis of adhesions.

There were 5 patients who suffered from pulmonary infarction, all of whom had thrombophlebitis. One patient with a pulmonary embolus died, and this complication was presumed to be the cause of death in another patient. One patient had 2 pulmonary infarcts while in the hospital and apparently recovered, but died suddenly at home 3 weeks later. The family doctor made a diagnosis of myocardial infarction although the patient was but 49 years of age and had not had any previous cardiac symptoms. It would seem that the most plausible explanation was that he had a pulmonary embolism.

There were 14 instances of medical complications resulting in 5 deaths.

MORTALITY

The mortality statistics are based on deaths in the hospital or on deaths within 30 days postoperatively whether the patients were still in the hospital or not. There were 19 deaths among the 216 patients operated upon, or an over-all mortality rate of 8.79 per cent. Of these patients, 9 died after definitive surgery, or a mortality rate of 6.56 per cent.

Three of the deaths after operation were due to medical conditions, namely, lobar pneumonia, myocardial infarct, and epileptic seizure. There was 1 death, proved at autopsy, due to pulmonary embolism, while another, we believe, resulted from the same condition. Postoperative gastrointestinal hemorrhage caused 1 death, although it is possible this patient had a gastric or duodenal ulcer. Shock, secondary to hemorrhage, in a patient who was merely explored and found to have an extensive lesion with hepatic metastases, resulted in another death. Two deaths resulted from peritonitis—one from the breakdown of the suture line at the anastomosis and the other as a consequence of mesenteric thrombosis with perforation of the ileum and peritonitis.

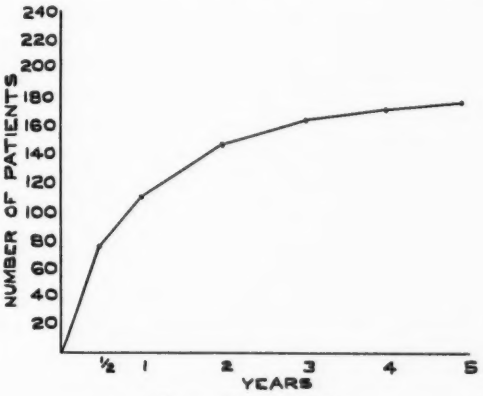

Fig. 2. Time of death.

MULTIPLE CARCINOMA

Three patients in this series had more than 1 carcinoma. One had a carcinoma of the cecum and a coexisting carcinoma of the transverse colon for which a hemicolectomy was done including resection of the entire transverse colon. One patient had coexisting carcinomas of the breast and rectum, the latter being inoperable. The third patient had a hemicolectomy for carcinoma of the cecum in August, 1948; and in November, 1952, she was found to have a carcinoma of the breast with axillary metastases.

SUMMARY

Two hundred fifty-two cases of carcinoma of the colon or rectum, which were seen over a 5 year period at the George F. Geisinger

Memorial Hospital and Foss Clinic, have been reported.

The average age of the patients was 60.92 years, there being 136 males and 116 females.

The most frequent symptoms and signs presented by these patients were weight loss (average, 20.33 pounds), pain, a palpable mass, melena, weakness, constipation, and diarrhea.

The average duration of symptoms before a diagnosis was made was apparently 7.18 months, and there was an additional delay of 4.82 months before admission to the hospital for treatment.

Sixty-eight and one-half per cent of all the carcinomas of the large bowel were found in the rectum, rectosigmoid, or sigmoid.

The operability rate was 55.24 per cent, but resection was also performed for palliation only in an additional 8.06 per cent with extensive lesions.

Surgical technique has been referred to and the point made that there is a trend toward one stage open anastomosis without diversion of the fecal stream except in case of obstruction.

A preliminary report on 5 year survival statistics covering 120 consecutive patients with carcinoma who were followed for the 5 years preceding June 1, 1953, is included. The over-all survival rate was 25 per cent, and the resectability survival rate was 42.86 per cent.

The majority of deaths following operation occurred in the first 2 years.

Thirty-one and one-half per cent of the patients operated upon had some postoperative complications of varying degrees of seriousness. Approximately half were due to urinary retention, cystitis, and the "neurogenic bladder," following excision of a rectal carcinoma.

There was a total of 19 deaths in the entire series, or an over-all operative mortality rate of 8.79 per cent. Of the patients on whom resection was carried out the mortality rate was 6.56 per cent.

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EDITORIALS

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CO-OPERATIVE TRAINING PROGRAM IN SURGERY BETWEEN VETERANS AND CIVILIAN HOSPITALS

RESIDENCY training in surgery is a matter deserving continual thought and reassessment. Excellent discussions on various phases of this subject have recently appeared as editorials in SURGERY, GYNECOLOGY AND OBSTETRICS by Jonas and Glover. Jonas' comments on the advantages of co-operation between civilian and veterans' hospitals are particularly apropos at this time. An increasing number of patients, formerly admitted to civilian teaching hospital ward services, are now being admitted either to veteran hospitals or as private cases under insurance plans. Glover discusses the difficulty in attaining certain ideals in a residency training program as a result of too few staff or ward service beds to provide adequate teaching material.

In the development of the graduate training program in surgery at the Massachusetts Memorial Hospitals, Boston, a joint program with the Veterans Administration Hospital, Providence, Rhode Island, was established in order to utilize the vast amount of clinical material existing in a Veterans Hospital of this size. This plan is most successful and of mutual benefit to all concerned. As a result of discussions between Dr. Reginald Smithwick, Chief of Surgery of the Massachusetts Memorial Hospitals, and Dr. Philip Cooper, Chief of the Surgical Service of the Providence Veterans Hospital, means of working out the details of such a program were found. The full co-operation of Dr. William J. Sullivan, Manager of the Providence Veterans Hospital, and the Veterans Administration staff in Washington in charge of graduate training, assisted greatly in paving the way for this liaison. Only through a Veterans Administration staff with vision and determination to utilize the available material for such training programs will new programs be begun or the present ones continued.

Each co-operative effort of this type has to be adapted to the peculiar needs of the training programs involved. No two programs are exactly alike. Administration of each through a deans' committee made up of representatives, at the highest level, of one or more medical schools assures efficiency and flexibility for each separate locale. The appointment of consultant and attending surgeons from the staff of the affiliating civilian hospital and medical school brings about closer integration as well as the stimulation of research activities and investigative projects available from the large amount of clinical material.

In all instances where feasible, a combined program is of benefit both to the civilian

teaching hospital and the Veterans Administration hospital. At times, however, a Veterans Administration hospital, even when operating under the auspices of a deans' committee, will prefer to have its own independent program. This may be the case even when the teaching hospitals, associated with the medical schools in question, supply the necessary consulting and attending surgeons for the veterans program while their own teaching hospitals may lack adequate clinical material at the ward service level.

A residency training program in general surgery in a Veterans Administration hospital, without other hospital association, has available abundant clinical material in certain fields and a deficiency in others as has been pointed out by Jonas. There is very little, if any, gynecology, surgery of trauma, and no contact with private patients. Experience in all of these fields is of vital importance in achieving a well rounded training. Hence, Veterans Administration Hospitals conducting residency training programs are really not in a position to take the responsibility for the complete training of a surgeon and need outside affiliations to supplement shortcomings in material. Besides, the facilities of the veterans' hospitals can be made of greater benefit to more men in graduate training if they are directly linked to the surgical training program of a civilian teaching hospital rather than remaining an autonomous unit.

With the changing economic situation in recent years, particularly the development of medical insurance plans, as well as the availability of the Veterans Administration hospitals in certain areas, the number of patients entering the ward surgical services of many civilian teaching hospitals is decreasing. While graduate training programs for internal medicine and its related specialties can be well run by utilizing private patients, if necessary, it is generally recognized that surgical training programs cannot be ideally conducted unless there is an adequate supply of patients of the "ward" status available for the house service. Private cases can be utilized for certain aspects of surgical training but only in a limited capacity. Hence, surgical training programs in civilian hospitals need the clinical material available in Veterans Administration hospitals. This is particularly true if one attaches credence to the recent reports emphasizing more physicians in all categories will be needed during the next 15 to 20 years to keep pace with the increasing population.

To some extent, the Veterans Administration Hospital at Providence is utilized for teaching of students in the Boston University School of Medicine. Due to the distance and time factor (40 miles, 1 hour by train), it is not considered wise to include the Veterans Hospital at Providence with those regularly used in Boston for fourth year teaching. However, a fourth year elective at Providence is being offered for students who wish to reside at the hospital. In the future, more fourth year students may come to realize the advantage of living in a hospital and gaining closer contact with the patients and the resident staff. Regular fourth year clinical clerks having daytime assignments in the various teaching hospitals do not have such an opportunity to enhance their surgical knowledge. As has been pointed out, oftentimes the most interesting surgical problems occur at night.

Hence, the civilian teaching and the Veterans Administration hospitals should and can attain a close affiliation in graduate and undergraduate teaching. Obviously, whenever possible, the type of material which is found in city hospitals, especially accident and fracture cases, should be integrated into graduate training programs. Rotations through the fracture and neurosurgical services of the

Boston City Hospital, as a result of the cooperation of the chiefs of these services, has been possible for those in the surgical program of our hospital. The economics of the present and foreseeable future indicate the best graduate programs will result from use of the best material available from the ward services of private civilian teaching, veterans, and city hospitals. Progress may be slow in fitting the various pieces into the picture in any given location. Success will come eventually if those in charge of the various sources of material to be integrated will adopt the attitude that the important consideration is the most effective use of the material at hand in the interest of the surgeons of the future.

GEORGE P. WHITELAW.

REVASCULARIZATION OF THE ARTERIOSCLEROTIC EXTREMITY

THE problem of increasing circulation in an arteriosclerotic extremity is based on the assumption that such regional increase is possible and justifiable. While arteriosclerosis is certainly a diffuse vascular disease, segmental stenoses and occlusions occur at points of stress with an elsewhere relatively undamaged vascular tree and such areas of stress are frequent in the lower extremity. While nutritional, biochemical, and hormonal studies may prevent or decelerate the progress of peripheral arteriosclerosis, there is to date no effective way permanently to increase the circulation to an ischemic extremity by other than surgical means. This rather broad statement is made in spite of the unprecedented appearance of lipotropic drugs, diets, and vasodilators. The latter drugs have limited use in acute arterial occlusions given intra-arterially but their effect is most evanescent and can only tide the extremity over a temporary, critical situation when it is unprepared to cope with an acute arterial occlusion at a critical point such as at aortic, femoral, or popliteal bifurcations.

There are an inestimable number of patients suffering from a subclinical or hardly recognized atheromatous stenosis of major arterial pathways. The progress of this lesion is gradual and highly variable. However, a major number of acute ischemic catastrophes occur in such arteriosclerotic limbs caused by a thrombotic occlusion of the stenosed segment. Trauma, hypotension, and hemorrhage may be some of the factors responsible for the acute thrombosis. Other limbs develop a slow gradual compensation for the obstruction of their major arterial pathway by developing a sufficient number of collateral channels. An injury to these channels or a closure of a distal segment of a patent but nonpulsatile artery below the level of obstruction may again seriously endanger the viability of a sclerotic but well compensated peripheral vascular tree.

A third group of patients suffer from claudication on exercise and it is well to remember that the site of muscular pain frequently denotes the level of occlusion. Thus iliac artery stenosis will cause pain in the lower back, buttocks, and thigh, femoropopliteal occlusion gives pain in the calf whereas the numb, painful sole of the foot is encountered in low occlusions of the posterior tibial or plantar arteries.

The removal of the occluding thrombus and its atheromatous wall restores the patency of the main artery. It cannot, of course, alter the course of the disease except for changes occurring distal to an arterial occlusion. Sympathectomy should still be regarded as a potent weapon to decrease vascular resistance in the collateral bed and to increase the critical closing pressure of an artery, i.e., to prevent collapse of the artery because of the low intraluminal pressure distal to the obstruction. It

is true, that the indications for sympathectomy in peripheral arteriosclerosis have been pushed too far in many places and that a combination of major arterial occlusion combined with advanced arteriolar sclerosis cannot be helped but possibly harmed by this operation. But this simply means that the general surgeon into whose domain sympathectomies, and particularly lumbar sympathectomies, are gradually passing must understand vascular disease which can readily elude or deceive those who only see it in the operating room.

Removal of an occluded segment, accurately localized and delineated by arteriograms may be followed by autogenous or homologous vein grafts. The superficial femoral artery is particularly suited to restoration of its patency by such means. Iliac stenoses or occlusions can be reamed out or replaced by venous graft but the occlusions of the aortic bifurcation need frozen homologous grafts obtained from an artery bank.

The future development of these banks will depend on availability of human specimens, on the ratio of demand versus supply, on possible simplification of methods of preservation, and perhaps on the successful use of animal material or plastic substances.

Certainly 10 years from now, unless arteriosclerosis disappears in the meantime, the replacement of closed arterial segments by viable or nonliving tubes will widely engage the surgeon throughout the country. Strangely enough, Carrel's work took 50 years to find wide clinical application but no one can yet speak authoritatively on the ultimate fate of vessel transplants and reamed out segments as well.

As 2 to 3 year follow-up studies come in, the percentage of patency is encouraging but allows room for much improvement; nor is it clear that vascular sclerosis does not progress elsewhere at such a rate as to make the patency of an isolated segment irrelevant. The patient with a restored, intensely pulsating posterior tibial artery may continue to die of vascular accidents as expressed by the gloomy Lancisi in 1707: "I have always wondered how it is that what we call life, that delicate and finespun fabric made up of fluids and solids, now ingeniously interwoven, now quite discontinuous, does not always break down in an instant from a disease quite unforeseen. How often is that fabric frayed to a thread by the slow wear and tear of age."

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THE BOOK SHELF

ROBERT BURNS AND HIS HEART

ESTHER H. VINCENT, Evanston, Illinois

ABOUT a third of a mile north of the old Alloway Kirk, near the banks of bonnie Doon, stands the two-roomed clay cottage which a dark, serious-minded young gardener, William Burnes, once built with his own hands for his bride, Agnes Broun. Agnes, red-haired and brown-eyed, was the vivacious daughter of a tenant farmer, could read but could not write, and had stored in her retentive memory all the songs and ballads of her romantic country. Both William and Agnes were filled with the religious vigor of old time Scotch Presbyterianism and were steadfastly trained in the ways of honesty and thrift. The family name evolved from the original Burness of Kincardinshire to the Burns eventually used by son Robert to accord with the Ayrshire pronunciation.

Robert, first of their seven children, was born on a blustery January day of 1759, and so severe was the wind that when he was but a few days old, the roof flew off their "clay biggin" and mother and baby had to be carried to the house of a neighbor, there to stay for the week it took to repair their home.

William Burnes had been a nurseryman and gardener for various landowners in the vicinity, but when Robbie was seven, the family moved to near-by Mount Oliphant and there rented a stubbornly unproductive little farm. Schooling was necessarily meager and intermittent, but the child had unusual ability and ambition, together with a truly phenomenal memory. In addition, he was fortunate in being brought up in a home where books and learning were valued.

When unable to afford even the cheap educational facilities of Ayrshire, the father somehow contrived to get a few books, and at the end of a tired day he would teach his bairns by candlelight, trying to give them not only love of learning but something of his own religious faith and courage. It is this picture that we see in "The Cotter's Saturday Night."

Robbie owed much of his personal magnetism to his attractive young mother, while from his somewhat dour father, he got tenacity of purpose and an unfortunate tendency to melancholy. During the 11 difficult years at Mount Oliphant, the young boy is said to have had numerous bouts of nervous depression and dull headaches at night, and later to have suffered from cardiac palpitation with feelings of faintness and suffocation. Both he and his next brother, Gilbert, did work too hard for growing lads, and Robbie, as eldest, no doubt felt the strain of his position in the family constellation as he was crowded upward into responsibility by six younger children. At the age of 13 he assisted in the threshing of the grain, and at 15 was the principal laborer on the servantless farm. The father, not too young when married, was now worn from hard labor and the stress of poverty. The stony little farm rewarded but feebly the efforts of one adult invalid and two immature boys, and much of Robert's later physical and nervous illness can be traced to this period.

When he was 18, the family finally freed itself from the wretched little farm at Mount Oliphant and moved to a slightly better one at Lochlie. This farm lay in a hill-surrounded depression, even now somewhat swampy, and at that time entirely undrained. The work was still backbreakingly hard, but the social life of near-by Tarbolton was pleasant, and the lad lived a fairly comfortable life for the next 4 years. He had a genius for friendship, which he was now able to cultivate, along with his lifetime attraction for the lassies.

Midsummer of 1781 found him at Irvine experimenting with flax-dressing and finding the work too confining for a youth accustomed to

outdoor life. Here he had the first of the several nervous breakdowns that were often to plague him. So melancholy were his letters home that his father came from Lochlie to help him. Robert wrote: "The least anxiety or perturbation in my breast produces the most unhappy effect on my whole frame." The thought that he might soon die gave him much comfort. He wrote a poem, "Prayer in Prospect of Death," which begins,

"O Thou, unknown almighty cause of all my hopes and fear,
In whose dread presence ere an hour, perhaps I may appear"

After his business partner proved to be a scoundrel and their little shop burned, Robert returned to Lochlie.

The family was now in dire straits. The American Revolution had had a bad effect on Scottish economy; many people lost all they had and were cold and hungry. In addition there were freezing storms with sad results for the crops. William Burnes, sick and prematurely old, tormented by unexpected and humiliating debts, slowly faded away, dying the following winter of "a phthisical consumption."

Salvaging what they could, Robert and Gilbert Burns rented another farm, Mossgiel, which with its thick clay earth was no exception to their poor luck in agriculture. In the late spring and summer of 1784 Robert had a severe physical breakdown, probably an early manifestation of a frequently recurring heart condition. In his "Commonplace Book," he wrote of his illness:

"A prayer, when fainting fits, & other alarming symptoms of a Pleurisy or some other dangerous disorder which indeed still threaten me, first put Nature on the alarm."

Burns's physician at this time was Dr. John Mackenzie, a young man of his own age, a surgeon in Mauchline. Dr. Mackenzie had attended William Burnes during his last illness and had become interested in the family with its general culture so far above its economic level. Fellow Masons, he and Robert became good friends, their favorite topic of conversation being the origin of morals. Mackenzie was one of those who helped Burns get his poems published and who eased his path to Edinburgh. Many years later he attained high magisterial honors at Irvine and was one of the founders of the Irvine Burns Club.

Nevertheless, he knew little of heart disease, and in his way played as much havoc with Robbie's heart as did the bonnie lassies in theirs. He prescribed cold baths and continued farm work. In spite of this, the naturally robust Burns got over the attack with its accompanying "hypochondria." But the illness left its mark!

Occasional poems concerning his depressed emotions, such as "Prayer under Pressure of Violent Anguish," and "Winter—a Dirge," may have relieved his tensions somewhat. Like others of us, he sometimes had dental difficulties, and during one painful experience he produced his "Address to the Toothache,"

"My curse upon your venom'd stang,
That shoots my tortur'd gums alang;
And thro' my lugs gies mony a twang,
Wi' gnawing vengeance;
Tearing my nerves wi' bitter pang,
Like racking engines!"

The names of several physicians are on the list of subscribers to the first edition of Burns's poems —Mr. John Bell, surgeon, Dr. Henry Cullen, Dr. Andrew Duncan, Dr. James Gregory, Dr. Alexander Monro, Mr. John Rae, surgeon, and Dr. Alexander Wood. Having achieved authorship, the "unlettered plowboy" went up to Edinburgh and shared a rented room with a friend. "Auld Reekie" was sociably appreciative and soon Burns was the lion of the hour. At this time he was a splendid figure of a man, five feet ten, strong and robust, with a simple dignity which gave polish to his country manners. His glowing dark eyes were his chief asset, but his face was expressive of his modesty, good sense, and absorbing interest in his fellowman.

A curious friendship sprang up between Burns and Dr. John Moore, surgeon and author-traveller, and father of Sir John Moore of Corunna. Dr. Moore lived in Glasgow and the two men never saw each other, but corresponded heartily for 4 years. One of Burns's letters was the famous autobiographical one, dated Mossgiel, August 2, 1785, which formed the basis of all future biographies. It was Dr. Moore who advised Burns to write in English rather than in the Scottish dialect, but fortunately the poet did not take the advice.

As fascinating interludes to his Edinburgh sojourn, Burns went on several horseback tours of the neighboring countryside, and on one of his Highland tours he had as companion, young Dr. James M'Kittrick Adair, son of an Ayr physician. On another trip Burns's horse fell with him, bruising him so badly that he was nursing his injuries for weeks.

Returning to Edinburgh for a second winter, Burns lived more quietly, occasionally suffering from fits of restless depression, which he called his "bitter blue-devilism." Publisher troubles further distressed him, and he had to eke out his

slender income by constant writing for *The Scots Musical Museum*, adapting and fitting new words to old Scottish tunes.

A friend at this time was Dr. James Gregory, leading Edinburgh practitioner and successor to Cullen on the Medical Faculty of the University, a witty but somewhat irascible associate of the literary elite of the town, and much interested in Burns as a fine subject for the psychology of genius. Dr. Gregory was the author of the then popular "Conspectus Medicinae Theoreticae," but is now best known for the rhubarb powder which bears his name. It was he who recommended the poems of Mrs. John Hunter to Burns, and who saw fit to criticize some of Burns's poems, especially "The Wounded Hare." Burns is said to have exclaimed: "Dr. Gregory is a good man, but he crucifies me."

Due to the awkwardness of a drunken driver, Burns was thrown from a coach and sustained a sprained knee which laid him up for several weeks, and, indeed, never did really heal, although Dr. Gregory and his surgical consultant, "Lang Sandy Wood," did their best. Dr. Alexander Wood was a lanky, kindly, and rather quaint individual, a man after Burns's own heart. A simple but gifted surgeon, he shared Burns's love of children and animals, even cherishing a pet lamb. Dr. Wood urged Burns to write the "Elegy on the Death of Lord President Dundas," and personally delivered the poem and accompanying letter to his Lordship's son, only to have the poem completely ignored, much to Burns's chagrin. It was Wood who later recommended the job-hunting poet to the Commissioners of Excise.

Altogether Edinburgh was a brilliantly satisfying but nevertheless disturbing experience for the glamorous poet. He was emotionally stirred on every hand, and between his poetry writing and the bonnie lassies, he had an exciting and not always happy time. Burns seems to have had an extraordinary attraction for women, and, as Robert Louis Stevenson says, he valiantly battered himself into warm affection for any girl who loved him. But he was an imperfect Don Juan, for he lacked the sinister courage to desert the victim, and was consequently perpetually entangled. Furthermore, he tenderly loved and cared for those of his children whose mothers would part with them.

Knowing that his dazzling popularity with the literary set of Edinburgh would not last, he set about renting another farm, Ellisland, and at the same time applied for a job as exciseman. Since he badly needed a wife to help him on the farm, he finally married the faithful Jean Armour and settled down again to hard physical labor.

But Ellisland was another agricultural mistake. Its 172 acres of poor soil are none too alluring even today, and its atmosphere of fevers and rheumatism was none too good for Robbie. Jean and her then only surviving child, Robert, stayed in Mauchline until Burns could build a new house to replace the old dark, dank shack, where he was "only preserved from being chilled to death by being suffocated with smoke."

Burns had seldom been free from illness since his overworked adolescence at Mount Oliphant, suffering frequent attacks of fever and "colds" accompanied by severe "hypochondria." Now, trying to manage his poor little farm and riding about the country in all weathers as a gauger, he used up his slight reserves. He brought in his first harvest, "though I am scarce able to hold up my head with this fashionable influenza, which is now the rage hereabouts." In another letter he wrote, "My knee, I believe never will be entirely well; and an unlucky fall this winter has made it still worse." Again, "I am so hurried and fatigued with my Excise-business that I can scarcely pluck up resolution to go through the effort of a letter." In addition, he had nervous headaches trying to make one guinea do the work of three.

In 1790 he was reasonably comfortable, but in 1791 he fell with his horse, injuring both hand and arm. In March, just at spring plowing, he fractured his arm. Autumn found him laid up, as in Edinburgh, with a bruised leg on a stool. Nevertheless it was at Ellisland that he somehow found time and energy to compose some of his best poetry. Here he wrote "Tam o'Shanter" and many fine lyrics, rescued "John Anderson My Jo" from disreputability, and glorified "Auld Lang Syne."

Having rid himself of the Ellisland lease, Burns moved his wife and their three living children (all under 6) to Dumfries, where his two illegitimate daughters joined them later and grew up as members of the family. In 1792 Jean bore a daughter, whose frail health was a source of deep anxiety to her affectionate father. In 1793 the family moved to a larger house on what is now Burns Street. Here Burns's salary as an exciseman enabled them to live in some comfort.

Burns still did not regard himself as an invalid, although his activities were now rather limited, and he rested a great deal. After a few weeks of the old depression, he renewed his zest for living, made new friends, and, in a resurgence of creative power, wrote some of his greatest poems. But

early in 1794 he came close to another nervous breakdown and was not able to so much as lift his hand to a pen. However, he got over it, took a short vacation tour of Galloway, and again took up his excise duties, this time as supervisor.

Burns always wanted his wife and children to be well dressed and well fed, although he saw to it that the family lived within his income. But now his whole budget was upset and he experienced frightening financial difficulties when he had to pay a note which he had endorsed for a defaulting friend. The stress and strain were almost more than he could bear, but eventually he and his finances returned to normal.

He took an active part in civic affairs, joining in all of the political and religious animosities of the time, sometimes unconsciously making enemies by his caustic wit. In January, 1795, he joined a group of citizens in a petition to organize the Royal Dumfries Volunteers, and was regular in attendance at drills and at directors' meetings. But in September he was overwhelmed with grief at the death of his youngest daughter. And in December he himself was seriously ill with fever, grew better in February, and worse in April. His physicians termed his arthritis, "flying gout."

In July, Dr. Maxwell recommended sea bathing and country life, and so poor Burns betook himself to Brow, 24 miles away on the Solway Firth. There he wrote to Alexander Cunningham:

"Alas! my friend, I fear the voice of the Bard will soon be heard among you no more! For these eight or ten months I have been ailing, sometimes bedfast & sometimes not; but these last three months I have been tortured with an excruciating rheumatism, which has reduced me to nearly the last stave.—You actually would not know [me] if you saw me.—Pale, emaciated & so feeble as occasionally to need help from my chair—my spirits fled! but I can no more on the subject—only the Medical folk tell me that my last & only chance is bathing & country quarters & riding."

Returning shortly to Dumfries, all the worse for his sea bathing, he felt himself so near death that he wrote to his father-in-law asking that Mrs. Armour come immediately to care for Jean, who was about to have another child. Three days later, on July 21 he was dead. He was only 37.

Dr. William Maxwell, his last physician and his very good friend and neighbor, had gone to French medical schools and had become so enthusiastic over the French Revolution that he joined the Republican Army and served as one of the guards at the execution of Louis XVI, actually dipping his handkerchief in the royal blood. He was of enough distinction to be mentioned by Burke in the House of Commons. Early in 1794 he began practice in Dumfries and shared leadership with Burns in a small group of Liberals. Burns's little son, born on the day of his father's funeral, was named Maxwell. The doctor joined other friends in arranging for the support of Jean and the children.

Burns's last days were filled with unwarranted financial anxiety. He worried about his family's welfare, he worried about the bill for his volunteer's uniform, and he had had hallucinations about being in the debtor's prison. But he was never in danger of bankruptcy.

Nor did he die of alcoholic excess and venereal disease, as stated by his first biographer, the well meaning but badly misled Dr. James Currie. Due to the many false statements and insinuations found in his "Life of Burns," Dr. Currie has later been almost as maligned as his subject. A literary Scotch physician of distinction, James Currie had settled down in Liverpool after an adventurous experience in America. It was he who introduced the clinical thermometer into practice, and long before Brand of Stettin, Dr. Currie had used cold baths in the treatment of typhoid fever, checking his results with the thermometer. His book, *Medical Reports*, published in 1798, was soon neglected and forgotten, but S. Weir Mitchell considered it a work of "absolute genius." Like Burns, Currie was a Liberal, but unlike him, he was also a fanatical temperance reformer. He died in 1805 at the age of 49, having been afflicted with both tuberculosis and heart disease, the latter brought on by rheumatic fever acquired while he was a student at Edinburgh. He saw Burns only once in his life (a brief meeting on a street in Dumfries) but he generously wanted to be of help to Jean and the children. So he edited the "Poems" and wrote the "Life," depending on such information as he could get from friends and relatives of the Burns family. Unfortunately, he got most of it from Syme and Maxwell, who unaccountably gave him the wrong impression. Also unfortunately, he himself was one of these people who think that any man who drinks at all is inevitably an alcoholic and probably a libertine. And so he arranged the "facts" of poor Burns's life to fit his own theories. Since his was the first biography and since he was so distinguished a man, subsequent biographies naturally continued the legend of an alcoholic Burns. The benevolent Currie died in blissful ignorance of the harm he had done.

Much was made of the story of a January 1796 carousal at the Globe Inn, Dumfries, when Burns was said to have fallen into a drunken sleep in the snow as he was trying to get home, the exposure leading to his eventual death. It is now known

that Burns was very ill in bed at the time and could not possibly have gone to the Inn even if he had wished. It has also been proved from letters and personal testimony of his associates that the poet drank somewhat less than the average man of his day. His friends all agreed to his habitual sobriety.

As to the "accidental complaint," Burns is known to have had many love affairs, but always with socially acceptable lassies who took the initiative in the wooing. He had absolutely no dealings with women of the town. Furthermore, Jean showed no sign of any infection. And if Burns had been incapacitated by venereal disease, his work would have suffered, and the record of his activities, both physical and mental, shows that this was not so. In fact, some of his best poems were written during the last period of his life, including "O Wert Thou in the Cauld Blast," which he wrote practically on his death bed.

Independently of one another, several present-day physicians have gathered together all references to his health found in Burns's and his friends' letters. In his "Burns from a New Point of View," Sir James Crichton-Browne of Dumfries says:

> "Burns died of endocarditis, a disease of the substance and membrane of the heart . . . At Mount Oliphant, from his 13th to his 15th year the heart trouble was well declared . . . At Mossgiel in 1784 there was an exacerbation of the disease . . . It is characteristic of the mild types of this insidious form of heart disease from which Burns suffered, that its victims, until it is far advanced, are able to go about and take an active share in affairs, as if there was nothing the matter with them. But they are visited at different intervals during its course of 20 or 30 years by feverish attacks, significant often of another milestone on the downward journey, in which, with a quickened pulse, they become weak and qualmish, and are highly strung, nervous, and easily agitated. It is attacks of this kind that are occasionally tabulated in [Burns's] correspondence. . . . It will not, I think, be disputed that Burns died of rheumatic endocarditis."

Dr. Harry B. Anderson of Toronto writes:

> "The case was an ordinary one of rheumatism with heart complications, shortness of breath, faintness, weakness, rapid, irregular pulse (auricular fibrillation), and toward the end, fever, parched tongue, and delirium, presumably due to a bacteriological endocarditis which developed as a terminal infection."

Dr. Anderson further considers that the injury to Burns's knee, brought about by the coach accident in Edinburgh, was evidently the beginning of his arthritis, the injury localizing the rheumatism in that joint, from which it later spread. He also points out that there may have been focal infections in his teeth, since the dentistry of that period would not have discovered them, and we know that Burns suffered from toothache. Anderson concludes that in a person of Burns's type—physical and mental strength combined with an intense, nervous temperament, and given to rapidly varying moods —"it is common that mental and nervous stress, worry and other emotional disturbance, produce a characteristic group of symptoms: headache, sleeplessness, digestive disturbance, irritability, apprehensiveness, depression, etc." Also, there is the close relationship between Burns's various breakdowns with the hard work, privation and exposure of his youth, which predisposed him to rheumatic fever and endocarditis. There were significant symptoms at 15, a second serious illness at 22, and 3 years later, physical exhaustion and crippling illness.

Dr. Watson-Smith notes that in this condition painful arthritis is not a rare complication, nor anxiety and dreadful suspense at the last. Further, the medical profession in Burns's time was still "wandering in a state of mist" as far as heart disease was concerned. However, even if modern therapeutic measures had been known, it is improbable that Burns, with his family to care for, could have followed the regime. It may be added that in 1796 the stethoscope had not yet been invented, and the bacterial origin of disease was not suspected.

Although Burns was able to earn a fair living for his family by the close of his brief life, it was the grinding poverty and financial anxiety of his early youth that brought about the condition from which he died. And yet he was one of the greatest exponents of the dignity of that very poverty:

> "Is there, for honest poverty,
> That hangs his head, an' a' that?
> The coward slave, we pass him by,
> We dare be poor for a' that!"

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3. Snyder, F. B. The Life of Robert Burns. New York: Macmillan, 1932.
4. Stevenson, R. L. Familiar Studies of Men and Books. Some aspects of Robert Burns. New York: Current Literature Publishing Co., 1909.
5. Watson-Smith, S. The disease that killed Robert Burns. Brit. M. J., 1944, 2: 864.

REVIEWS OF NEW BOOKS

OCCASIONALLY a book is written which fills a particular need, and which fills it completely. Ponton accomplished this feat with his first edition of *The Medical Staff in the Hospital*,[1] and the present revision has strengthened the book by modernization. It should be required reading for all hospital administrators, officers and committee members of medical staffs, and officers of governing boards.

MacEachern points out that the author first formulated and published a method for auditing professional activities in a hospital. Ponton's chapter on this phase has been extensively revised in the light of experience although, regrettably, an explanation of the tissue committee as an essential for accreditation is not included.

An attempt has been made to show the effect of present day social security and prepayment insurance on the economy of hospital and staff relationship. The intern-matching program is explained, as is the value of certification by American specialty boards and membership in other qualifying bodies in granting staff privileges.

The addenda contain the requirements for hospital accreditation, approval for internships and residencies, and sample by-laws.

GEORGE W. STEPHENSON.

THE edition *Lehrbuch der Gynaekologie*[2] which appears 5 years after the previous one contains almost the identical number of pages and illustrations. In it, Martius has made many changes. He has given more attention to neurohormonal changes in women, to the modern treatment of pelvic tuberculosis and to early diagnosis of carcinoma.

In the discussion on early detection of carcinoma of the cervix, Martius describes the use of the colposcope and the value and importance of cytologic studies. For invasive carcinoma, which is limited to the uterus, the author prefers surgery followed by radiation therapy 8 weeks later. For cases in which the carcinoma has extended beyond the uterus, irradiation treatment is carried out. In the section on tuberculosis of the genitalia, the newer chemotherapy is described, including streptomycin, paraminosalicylic acid, thiosemicarbazon and isonicotinic acid hydrazide. In the section devoted to endocrinology, the author emphasizes that the use of female hormones should not be considered as simple substitution therapy, else there will be many failures.

The book is written in simple language and the advice given is in accord with that recommended by leading gynecologists throughout the world. In the entire book practical, helpful suggestions are made which indicate the vast experience of the author both as a gynecologist and as a teacher, for Martius is one of the foremost German obstetricians and gynecologists. There are a great number of beautiful and instructive illustrations, many in color. Nearly all are the work of Käthe Droysen, a very able and clever artist. The publishers, too, have helped to make this book an excellent one. There is no doubt that this edition will increase the great popularity of Martius' books in German speaking countries and elsewhere. There is now an Italian translation and a Spanish one in press.

J. P. GREENHILL.

THE reviewer has read the monograph *Diagnosis and Localization of Brain Tumors*[3] three times. The first time for general understanding, and the second and third times in analytic review. Each reading has been fruitful. The chapters on the "Blood-Brain-Barrier" and the "Cerebrospinal Fluid Barrier" should be studied by anyone interested in cerebral physiology. Two chapters devoted to the use of fluorescin and its radioactive components are worthy of careful reading. History, clinical application, technique, and general consideration including case reports are simply but adequately described. Analysis of the use of dyes and radioactive substances are discussed and analyzed in a very effective manner. One can not read this brief, compact monograph without being stimulated towards investigative channels with the realization that the biophysical and chemical consideration of cerebral pathology is becoming increasingly more important.

The title, *Diagnosis and Localization of Brain Tumors*, is somewhat misleading in that it suggests neurologic interpretation rather than techniques in biochemistry and biophysics. It is enthusiastically recommended to anyone interested in the field of neurophysiology and neurosurgery.

DAVID CLEVELAND.

THE improved second edition of *Surgical Pathology*[4] includes several additional topics, 124 new gross and microscopic photographs, and 7 replaced photographs. Two new chapters have also been incorporated, one dealing with the surgical lesions of

[1] THE MEDICAL STAFF IN THE HOSPITAL. By Thomas Ritchie Ponton, B.A., M.D. 2nd ed., completely revised by Malcolm T. MacEachern, M.D., C.M., D.Sc., F.A.C.H.A., F.A.C.P., LL.D., F.A.C.S. 373 pages with 57 illustrations. $7.25. Chicago: Physicians' Record Co., 1953.

[2] LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Med. Heinrich Martius. 3rd rev. ed. 414 pages, 446 illustrations. DM 49.80. Stuttgart: Georg Thieme Verlag, 1953.

[3] DIAGNOSIS AND LOCALIZATION OF BRAIN TUMORS; A CLINICAL AND EXPERIMENTAL STUDY EMPLOYING FLUORESCENT AND RADIOACTIVE TRACER METHODS. By George E. Moore, M.D., Ph.D. 217 pages, 66 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1953.

[4] SURGICAL PATHOLOGY. By Peter A. Herbut, M.D. 2nd rev. ed. 893 pages, 528 illustrations. $14.00. Philadelphia: Lea & Febiger, 1954.

the adrenal glands, and the other, by Bernard J. Alpers, Professor and Head of the Department of Neurology, Jefferson Medical College, dealing with the surgical disorders of the nervous system.

The text is clear, concise, and factual. Controversial items are treated briefly with a statement of prevailing thought. An attempt has been made to keep prolixity to a minimum—a commendable feature in a voluminous subject.

The references at the end of each chapter are numerous, and make readily available the pertinent references to more detailed analysis of the material presented.

The classification of the various diseases with complete and concise discussion of the numerous aspects of each has served to meet the ideals set forth by the author, ". . . to treat the subject from a regional viewpoint and summarize, as far as possible, the current ideas from the current literature."

Again, the book may be recommended without reservation to general surgeons and members of the allied fields. MARK C. WHEELOCK.

IN the second edition of *The Pathology of Trauma*[1] by Alan Richards Moritz, the author has maintained a "by what cause, by what manner, and by what means" method of exposition, and has judiciously correlated the pathologic physiology, and pathologic anatomy with clinical material, when the latter was available. Answers for the causal relation between disease and mechanical injuries are given when the evidence, empirically obtained, is available by the application of the elementary laws of physics —force, kinetic energy, and biochemistry.

The text contains ample evidence of the value of contributions of the morbid anatomist, the physiologist, the biochemist, and the physicist. Nonpenetrating wound of the abdomen as a cause of acute appendicular disease, perforation of hollow visci, hernia, and diabetes mellitus is neither categorically affirmed, nor denied. The method of discussion of this cause and effect relationship is such, however, that the reader is not left with the idea "the twain shall never meet." Chapters have been rewritten, and in several instances, material made available since publication of the first edition has been added. A new chapter, "The Medico-Legal Autopsy," is a welcome addition of especial interest to forensic pathologists, lawyers who represent industry, insurance companies, and public prosecutors in litigation concerning the dead body. Additions have also been made in the form of paragraphs added to a number of chapters. The paragraph covering crush syndrome is a clear and concise exposition of this relatively recently understood, or recognized disease.

A generous supply of photomicrographs, and diagrams are presented in appropriate parts of the text to enable the reader to follow the discussion. Significant additions have been made to the chapter on "Mechanical Injuries to the Central Nervous System." The mention of names of "workers in the field," and the subject matter of their contribution, such as "magnitude of impact influences the size and shape of zone of traumatized tissue . . . ," Spatz; "cerebral concussion is essentially a transient state," Trotter; "cerebral concussion is probably a rapid acceleration of the head," Denny-Brown and Russell; "fatal hemorrhage due to distortion and compression of tissue in the midbrain and upper pons may occur with trauma to the sides and vertex of the head," Courville, are a few examples of the use of terse, but ample, statements which provide the reader with information easy to comprehend and easy to retain. This chapter also contains an excellent discussion of the histologic changes associated with degeneration, regeneration, hemorrhage, necrosis, and scar formation as the aftermath of cerebrospinal trauma. An excellent set of references is provided in an extensive bibliography at the end of each chapter, and yet the subject matter of each chapter is sufficiently inclusive to make use of the bibliography a rare occasion.

Because of the eminence of the author in the fields of forensic pathology, and general pathology this book is highly recommended to those employed in the field of forensic pathology, and teachers of general and special pathology. To the clinician and student this work will serve as a clear and interesting exposition of the essentials of pathology of trauma in much greater detail than can be found in any textbook on pathology or surgery. J. J. KEARNS.

MANY ramifications of the field of hematology are covered in a delightfully concise manner in *Disorders of the Blood*.[2] This is achieved without jeopardizing the exhaustive coverage demanded of such a work, through constant reference to a full, but critically selected bibliography. The marked activity in this field during the 3 years since the appearance of the last previous edition has been covered very adequately, and in only 87 additional pages. This has necessitated numerous changes in the entire book, with especially extensive revision of those portions dealing with coagulation, hematopoiesis, and hemolysis. In a field marked by confusion of terminology, the reader owes a profound debt of gratitude to the authors, who are unusually apt at clarifying and correlating variations in nomenclature.

The authors' approach has been from the clinical viewpoint. In the first few chapters the basic principles of hematology are developed briefly in standard textbook fashion, but early in the book the emphasis changes to development and amplification of hematologic concepts through descriptions of reported clinical observations and basic investigative

[1] THE PATHOLOGY OF TRAUMA. By Alan Richards Moritz, M.D. 2nd enl. rev. ed. 414 pages, 126 illustrations. $8.50. Philadelphia: Lea & Febiger ,1954.

[2] DISORDERS OF THE BLOOD; DIAGNOSIS: PATHOLOGY: TREATMENT: TECHNIQUE. By Sir Lionel E. H. Whitby, C.V.O., M.C., M.A., M.D. (Cantab.), F.R.C.P. (Lond.), D.P.H., and C. J. C. Britton, M.D. (New Zealand), D.P.H. 7th ed. 856 pages, with 20 plates and 106 text-figures. $9.50. New York: Grune & Stratton, 1953.

measures. Continuity is furthered by grouping technical procedures in the long, last chapter.

The stature of this work is such that it must be familiar to the hematologist, should be known to the medical student, and its good index enhances its value to those who enter this field only occasionally with a specific problem. FRANK R. ELLIOTT.

EXPERIMENTING on rabbits, the author[1] studied the effect of cortisone on the development of adhesions about injured tendons and its influence upon the process of healing after suture of divided tendons. After making an extensive review of the somewhat contradictory literature on the subject, he described his own method for the production of peritendinous adhesions and for measurement of their strength. He showed that a standard traumatism of the tendon of the extensor hallucis longus of the hind leg of the rabbit caused peritendinous adhesions of uniform strength. After a fixed period of time the traction necessary to pull a section of the tendon out of its bed was measured in a thread tester. The sources of error in his experiments were carefully reviewed and tested.

His experiments showed conclusively that an injection of 1 to 5 milligrams of cortisone per kilogram of body weight greatly reduced the strength of the adhesions formed. The reduction was more noticeable when the cortisone treatment was begun prior to or immediately after the operation and maintained for several weeks than when it was begun later or maintained for a shorter time. When the adhesions formed around a traumatized tendon were freed, the new adhesions formed afterward were much weaker when the animal was given cortisone than when it was omitted. The differences between the animals treated with cortisone and the controls were very distinct, not only as regards strength, but also as regards gross and microscopic appearance.

A number of experiments with locally applied cortisone did not reveal any convincing difference between the test animals and controls. Probably the vehicle in which the cortisone was suspended had an irritating, adhesion-favoring effect in itself.

The effect of cortisone on the course of healing in divided tendons was studied by dividing and suturing the aforementioned tendon in a few cases and the achilles tendon in others. The tissue was not so well consolidated at the site of division as usual, but healing took place.

The author concluded his careful and critical study with a discussion of a number of clinical aspects and pointed out that particularly in the case of "tenolysis, the depressive effect of cortisone on tissue reaction might be utilized to advantage."

This work provides an experimental foundation on which to base a clinical study. It also describes a new and valuable method to use in experimental work on the problem of tendon adhesions.

ERIK MOBERG.

THE monograph *Peptic Ulcer*[2] is a beautifully illustrated discussion of the ulcer problem by a man who has had a long and extensive experience, and who insists that he is but the mouthpiece of a large team of associates and assistants who, by their collaboration, have given him the knowledge from which he writes. An excellent discussion is provided of the physiology of gastric secretion and its relation to the ulcer problem. References to important papers are provided at the close of each chapter. An extensive account is given of the production of peptic ulcer in experimental animals, and the relation of this work to the problems encountered in man is clearly developed. This fine contribution to the literature on peptic ulcer by an experienced surgeon who has kept abreast of the experimental work in his field will be welcomed by general surgeons, by gastroenterologists, and by all physicians who are interested in this common and distressing disease. LESTER R. DRAGSTEDT.

THE volume entitled, *Total Values of Blood Volume, Hemoglobin, Proteins, and Extracellular Fluids in Surgery*,[3] is a compilation of work done as part requirement for a doctoral degree, and although much concerns a subject matter explored by others in various countries the painstaking recapitulation of details, the amassing of tedious laboratory data, and the wide variety of conditions investigated commend the investigator as a careful researcher.

There were 59 distinct disease processes in 169 patients which were studied, the standard normal being obtained from 18 cases. This includes the individual variation found in the male and female subjects. It was seen that in grave disorders, such as malignant tumors or chronic inflammatory conditions, there is a deficit reading in the tests ranging from 10 to 20 per cent. In the first 48 hours postoperatively there is a decrease in values but they usually revert to their original figure in approximately 72 hours. In shock, however, depending upon the degree, the readings may be from 8 to 42 per cent off normal.

The volume is prepared according to standard thesis from and is documented with many charts, figures, and grafts. The bibliography contains 289 articles and the protocol consisting of minute recording in each case comprises a goodly portion of the work. STEPHEN W. ZIEMAN.

[1]ACTA CHIRURGICA SCANDINAVICA. Supplementum 182. THE EFFECT OF CORTISONE ON THE FORMATION OF TENDON ADHESIONS AND ON TENDON HEALING; AN EXPERIMENTAL INVESTIGATION IN THE RABBIT. By Nils Carstam. 111 pages, 23 illustrations. Stockholm: Acta chirurgica scandinavica, 1953.

[2]PEPTIC ULCER. By C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.E., F.R.F.P.S. (Glas.). 287 pages, 89 illustrations. $8.50. Baltimore: The Williams & Wilkins Co.; Edinburgh, London: E. & S. Livingstone, Ltd., 1953.

[3]VALORES TOTALES DEL VOLUMEN SANGUINEO, HEMOGLOBINA, PROTEINAS Y LIQUIDO EXTRA-CELULAR EN CIRUGIA. (TESIS DOCTORAL). By Hipólito Durán Sacristán. Director: Profesor R. Vara López. 286 pages, 24 illustrations. Burgos, Spain: Secretariado de Publicaciones, Universidad de Valladolid, Facultad de Medicina, 1953.

PRACTICAL fundamentals that lead to rational and effective treatment in acute emergencies are stressed in the concise and well illustrated pocket sized manual entitled *Manual of Medical Emergencies*.[1] The scope of the text is broad and includes chapters on respiratory and circulatory emergencies, acute poisonings, allergic disturbances, comatose states, head injuries, psychiatric emergencies, and drug reactions. Specific drug therapy is outlined whenever indicated, and the procedures advocated are clearly and thoroughly described. Recommended drugs, equipment, and procedures are confined to those easily attainable, transportable, and workable.

Both medical and surgical house staff officers as well as the busy general practitioner should find this handbook valuable as a quick reference which can always be kept within easy reach. JOHN L. BELL.

[1] MANUAL OF MEDICAL EMERGENCIES. By Stuart C. Cullen, M.D., and E. G. Gross, M.D. 2nd ed. 278 pages, 34 illustrations. $4.50. Chicago: The Year Book Publishers, Inc., 1953.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

EL SIMPATICO Y LA NUEVA PATOLOGIA FUNCIONAL. By Dr. Miguel Lopez Esnaurrizar. 72 pages, and 15 documentos. Mexico: Union Tipografica Editorial Hispano Americana, 1954.

INTRODUCTION A LA PRATIQUE CHIRURGICALE DE LA HANCHE; RECHERCHES ANATOMIQUES PERSONNELLES DEDUCTIONS CHIRURGICALES PRATIQUES. By Jean Cheynel, 104 pages, 26 illus. 975 fr. Paris: G. Doin & Cie, 1954.

DIE NARKOSE; EIN LEHR-UND HANDBUCH. Edited by Prof. Dr. H. Killian and Prof. Dr. H. Weese. Assisted by Dr. W. Irmer and Dr. F. H. Koss, with the contributions of Prof. Dr. F. Hahn, Doz. Dr. W. Rummel, and Dr. R. Vormann. 1003 pages, 412 illustrations. DM 170, $40.50. Stuttgart: Georg Thieme Verlag, 1954.

PHYSICAL ASPECTS OF BETATRON THERAPY. By John S. Laughlin. 98 pages, 34 illustrations. $3.95. Springfield, Ill.: Charles C Thomas, 1954.

THE DIAGNOSIS AND TREATMENT OF THE INFERTILE FEMALE. By Fred A. Simmons, M.D. 83 pages, 8 illustrations. $2.50. Springfield, Ill.: Charles C Thomas, 1954.

TASCHENBUCH DER PRAKTISCHEN THORAXCHIRURGIE. By Dr. med. W. E. J. Schneidrzik. 325 pages, 70 illustrations, and 14 tables. Stuttgart: Gustav Fischer Verlag, 1954.

TRATAMIENTO MEDICO DE LA ULCERA GASTRICA Y DUODENAL: ACCION DE LA BANTINA. By Dr. Juan Nasio. 140 pages, 27 illustrations. Buenos Aires: Editorial "El Ateneo" Libreria, 1954.

DE ARDITIS NONNULLIS AC MIRANDIS MORBORUM ET SANATORIONUM CAUSIS. By Antonio Benieieni. The Hidden Causes of Disease. Translation by Charles Singer. With a biographical appreciation by Esmond R. Long. 217 pages, 5 plates. $6.75. Springfield, Ill.: Charles C Thomas, 1954.

MODERN PRACTICE IN ANAESTHESIA. Edited by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A. 2nd ed. 622 pages, 221 illustrations. $12.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1954.

ARCHIV UND ATLAS; DER NORMALEN UND PATHOLOGISCHEN ANATOMIE IN TYPISCHEN ROENTGENBILDERN. Atlas postmortaler Angiogramme. By Dr. J. Schoenmackers and Dr. H. Vieten. 203 pages, 145 illustrations. Stuttgart: Georg Thieme Verlag, 1954.

EINRICHTUNG UND ARBEITSWEISE EINER BLUTBANK. By Dr. Med. Habil. W. Heim and Dr. Med. Habil. P. Dahr. 382 pages, 36 illustrations. DM 33. Stuttgart: Georg Thieme Verlag, 1954.

RECENT ADVANCES IN CARDIOVASCULAR PHYSIOLOGY AND SURGERY. A Symposium Presented by the Minnesota Heart Association and the University of Minnesota. 132 pages, illustrated. $1.00. Minneapolis: University of Minnesota, 1954.

ANTIBIOTIKA-FIBEL; INDIKATION UND ANWENDUNG DER CHEMOTHERAPEUTIKA UND AUTIBIOTIKA. By Dr. A. M. Walter and Prof. Dr. L. Heilmeyer. 813 pages. DM 79. Stuttgart: Georg Thieme Verlag, 1954.

PERIPHERAL CIRCULATION IN MAN; A CIBA FOUNDATION SYMPOSIUM. Editors for the Ciba Foundation, G. E. W. Wolstenholme, O.B.E., M.A., B.Ch., and Jessie S. Freeman, M.B., B.S., D.P.H. Assisted by Joan Etherington. 219 pages, illustrated. $6.00. Boston: Little, Brown and Co., 1954.

BEYOND THE GERM THEORY; THE ROLES OF DEPRIVATION AND STRESS IN HEALTH AND DISEASE. Iago Galdston, M.D., Editor. 182 pages. $4.00. A New York Academy of Medicine Book. New York, Minneapolis: Health Education Council, 1954.

THE SURGERY OF PULMONARY TUBERCULOSIS. By James H. Forsee, A.B., B.S., M.D., F.A.C.S., F.A.C.P. 208 pages, 59 illustrations. $6.50. Philadelphia: Lea & Febiger, 1954.

ANESTHESIA IN GENERAL PRACTICE. By Stuart C. Cullen, M.D. 4th ed. 312 pages, 37 illustrations. $5.00. Chicago: Year Book Publishers, Inc., 1954.

GLANDULAR PHYSIOLOGY AND THERAPY. Prepared under the Auspices of the Council on Pharmacy and Chemistry of the American Medical Association. 5th ed., completely revised and rewritten. $10.00. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

PROBLEMS OF INFANCY AND CHILDHOOD. Transactions of the Seventh Conference, March 23 and 24, 1953, New York, N. Y. Edited by Milton J. E. Senn, M.D. 196 pages. $2.75. New York: Josiah Macy, Jr. Foundation, 1954.

NEW AND NONOFFICIAL REMEDIES CONTAINING DESCRIPTIONS OF THE ARTICLES WHICH STAND ACCEPTED BY THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION ON JANUARY 1, 1954. Issued under the direction and supervision of the Council on Pharmacy and Chemistry, American Medical Association. 609 pages. Philadelphia, London, Montreal: J. B. Lippincott Co., 1954.

ARREST OF BLEEDING; PHYSIOLOGY, PHARMACOLOGY, PATHOLOGY. By Jacques Roskam, M.D. 71 pages, 21 illustrations. $2.75. Springfield, Ill.: Charles C Thomas, 1954.

PROCESSOS INFLAMATÓRIOS DA JUNÇÃO COLÉDOCO-PANCREATO-DUODENAL; CONTRIBUIÇÃO AO SEU DIAGNÓSTICO E TRATAMENTO. By Plinio Bove. 462 pages, 100 illustrations. Sao Paulo, 1953.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

FRANK GLENN, New York, *President*
ALFRED BLALOCK, Baltimore, *President-Elect*

PRELIMINARY PLANS FOR 40TH CLINICAL CONGRESS CONVENTION HALL, ATLANTIC CITY, NEW JERSEY NOVEMBER 15 TO 19, 1954

THE July issue of SURGERY, GYNECOLOGY AND OBSTETRICS presented an overview of the entire Clinical Congress program. More detailed information on some of the sessions will be listed here, and, as the program takes shape, in subsequent issues of the journal. The entire program will appear in the October issue.

Increased emphasis will be given in this year's Clinical Congress to the special fields of surgery. The Advisory Councils of some surgical specialties have chosen subjects for their panel discussions which have a mutual interest for surgeons in some of the other specialties. These "Joint Sessions" will be held especially in urology, gynecology and obstetrics:

UROLOGY PANEL DISCUSSION SESSIONS

Wednesday, November 17

9:00–10:30 a.m.—The Clinical Management of Spinal Cord Injuries.
Moderator: GEORGE C. PRATHER, JR., Brookline, Mass.
Collaborators:
Orthopedic Surgery—WILLIAM G. KUHN, JR., New Brunswick, N.J.
Neurosurgery—FRANK H. MAYFIELD, Cincinnati.
Urology—HERBERT S. TALBOT, West Roxbury, Mass.

10:45–12:15 p.m.—Incontinence in Women.
Moderator: ALBERT E. GOLDSTEIN, Baltimore.
Collaborators:
Gynecology—JOHN C. ULLERY, Philadelphia.
Neurology—O. R. LANGWORTHY, Baltimore.
Urology—ROBERT B. MCIVER, Jacksonville, Florida.

Thursday, November 18

9:00–10:30 a.m.—The Abdominal Mass.
Moderator: ORMOND S. CULP, Rochester, Minn.
Collaborators:
General Surgery—ALTON OCHSNER, New Orleans.
Gynecology—ROBERT A. KIMBROUGH, JR., Philadelphia.
Pathology—ARTHUR PURDY STOUT, New York.
Urology—WILLIAM J. ENGEL, Cleveland.

Friday, November 19

1:30–3:00 p.m.—Postoperative Depletion States of Urological Patients.
Moderator: GEORGE F. CAHILL, New York.
Collaborators:
General Surgery—CARL A. MOYER, St. Louis.
Urology—JOHN A. BENJAMIN, Rochester, N.Y.; HOWARD I. SUBY, Boston.

GYNECOLOGY AND OBSTETRICS PANEL DISCUSSION SESSIONS

Wednesday, November 17

1:30–3:00 p.m.—Urologic Injuries in Pelvic Surgery, Their Prevention and Treatment.
Moderator: HOWARD ULFELDER, Boston.
Collaborators:
Urology—WYLAND F. LEADBETTER, Boston.
Gynecology—CONRAD G. COLLINS, New Orleans; HOUSTON S. EVERETT, Baltimore.

3:30–5:00 p.m.—Differential Diagnosis and Treatment of Vaginal Discharges.
Moderator: WALTER T. DANNREUTHER, New York.
Collaborators: HENRY CLOSE HESSELTINE, Chicago; ANDREW A. MARCHETTI, Washington, D.C.; JOHN PARKS, Washington, D.C.; WARD F. SEELEY, Detroit.

Thursday, November 18

1:30–3:00 p.m.—Peri-Natal Pathology.
Moderator: ALLAN C. BARNES, Cleveland.
Collaborators: GEORGE W. ANDERSON, Baltimore; M. EDWARD DABIS, Chicago; CHARLES H. HENDRICKS, Columbus, Ohio.

Friday, November 19

1:30–3:00 p.m.—Review of Modern Diagnostic Tests of Pregnancy.
Moderator: DONALD G. TOLLEFSON, Los Angeles.
Collaborators: EARL T. ENGLE, New York; LOUIS M. HELLMAN, Brooklyn; SOMERS H. STURGIS, Boston.

3:15–4:45 p.m.—Problems of Labor Related to the Myometrium.
Moderator: BENJAMIN TENNEY, JR., Boston.
Collaborators: DANIEL J. MCSWEENEY, Brookline, Mass.; BERNARD J. PISANI, New York; ALFRED L. POTTER, Providence, R.I.

NEUROLOGIC SURGERY PANEL DISCUSSION SESSION

Thursday, November 18

1:30–3:00 p.m.—Experiences in the Treatment of Intracranial Meningiomas.
Moderator: EDGAR F. FINCHER, Emory University.
Collaborators: FRANCIS C. GRANT, Philadelphia; GILBERT HORRAX, Boston; BRONSON S. RAY, New York.

Friday, November 19

1:30–3:00 p.m.—Electrolyte Balance and Postoperative Infections in the Neurosurgical Patient.
Moderator: E. S. GURDJIAN, Detroit.
Collaborators: EDWIN B. BOLDREY, San Francisco; J. LAWRENCE POOL, New York; HENRY G. SCHWARTZ, St. Louis.

ORTHOPEDIC SURGERY PANEL DISCUSSION SESSIONS

Friday, November 19

1:30–3:00 p.m.—Fractures of the Neck of the Femur.
Moderator: EDWIN F. CAVE, Boston.
Collaborators: JAMES A. DICKSON, Cleveland; CARROLL B. LARSON, Iowa City; MARCUS J. STEWART, Memphis.
3:15–4:45 p.m.—Soft Tissue Tumors of the Extremities.
Moderator: RALPH K. GHORMLEY, Rochester, Minn.
Collaborators: JOHN C. IVINS, Rochester, Minn.; E. H. SOULE, Rochester, Minn.; H. HERMAN YOUNG, Rochester, Minn.

PLASTIC SURGERY PANEL DISCUSSION SESSIONS

Friday, November 19

1:30–3:00 p.m.—Problems in Cleft Lip and Cleft Palate Repair.
Moderator: BRADFORD CANNON, Boston.
Collaborators: PRESTON C. IVERSON, Philadelphia; W. BRANDON MACOMBER, Albany; ROBERT E. MORAN, Washington, D.C.
3:15–4:45 p.m.—Reconstructive Surgery of the Nose.
Moderator: FRANK MCDOWELL, St. Louis.
Collaborators: JOHN B. ERICH, Rochester, Minn.; E. HORACE KLABUNDE, San Francisco; THOMAS W. STEVENSON, New York.

THORACIC SURGERY PANEL DISCUSSION SESSIONS

Friday, November 19

1:30–3:00 p.m.—Thoracic Surgery in the Aged.
Moderator: BRIAN BLADES, Washington, D.C.
Collaborators: JOHN H. GIBBON, JR., Philadelphia; EDWARD M. KENT, Pittsburgh; CHARLES W. THOMPSON, Washington, D.C.
3:15–4:45 p.m.—New Developments in the Surgery of Heart Disease.
Moderator: JULIAN JOHNSON, Philadelphia.
Collaborators: To be announced.

OTOLARYNGOLOGY SESSIONS

Tuesday, November 16

3:30–5:00 p.m.—Relationship of Blood Dyscrasias to Otolaryngology, and the Control of Bleeding.
Moderator: LOUIS H. CLERF, Philadelphia.
Collaborators: VICTOR C. MCCUAIG, New York; HENRY D. RENTSCHLER, Sayre, Pa.; LEANDRO M. TOCANTINS, Philadelphia.

Wednesday, November 17

9:00–10:30 a.m.—Symposium.
Congenital Diseases of the Larynx. DANIEL C. BAKER, JR., New York.
Borderline Malignant Lesions of the Larynx. F. JOHNSON PUTNEY, Philadelphia.
Carcinoma of the Mouth and Tongue, Including Hemihyoidectomy in the Performance of the Commando Operation. JOEL J. PRESSMAN, Los Angeles.
3:30–5:00 p.m.—Management of Sinus Disease.
Moderator: EDWARD J. WHALEN, Hartford, Conn.
Collaborators: EDWARD H. CAMPBELL, Philadelphia; FRED W. DIXON, Cleveland; I. JEROME HAUSER, Detroit.

Thursday, November 18

9:00–10:30 a.m.—Symposium.
Nasopharyngeal Fibroma. JOHN B. ERICH, Rochester, Minn.
Cancer of the Nasopharynx. DANIEL MILLER, Boston.
X-Ray Diagnosis of Lesions of the Nasopharynx. RODERICK L. TONDREAU, Philadelphia.

OPHTHALMOLOGY SESSIONS

Tuesday, November 16

1:00–3:00 p.m.—Panel Discussion on Surgical Management of Diseases of the Cornea.
Moderator: RUDOLF AEBLI, New York.
Collaborators: WILLIAM B. CLARK, New Orleans; HERBERT M. KATZIN, New York; BRENDAN D. LEAHEY, Lowell, Mass.; R. TOWNLEY PATON, New York.

Wednesday, November 17

1:00–3:00 p.m.—Panel Discussion on Minor Surgical Problems of the Eye and Adnexae.
Moderator: ROBISON D. HARLEY, Atlantic City.
Collaborators: IRVING H. LEOPOLD, Philadelphia; HOMER R. MATHER, JR., Latrobe, Pa.; JOHN M. MCLEAN, New York.

Thursday, November 18

1:00–3:00 p.m.—Panel Discussion on Selection of Operative Technique in Retinal Separation.
Moderator: HAROLD G. SCHEIE, Philadelphia.
Collaborators: PAUL AUSTIN CHANDLER, Boston; JOHN W. HENDERSON, Rochester, Minn.; WILLIAM F. HUGHES, JR., Chicago.

General sessions will be held Monday through Thursday, and will include panel discussions, symposia, and clinicopathology conferences. The opening session of the Congress will be held on Monday at 10 a.m., beginning with a panel discussion on "Benign Lesions of the Lower Esophagus." Moderator will be Richard H. Sweet of Boston. Collaborators will include William E. Adams, Chicago, Thomas H. Burford, St. Louis, John H. Garlock, New York, Herman J. Moersch, Rochester, Minnesota. A clinicopathology conference will follow from 1:30 to 3 p.m., with Robert C. Horn, Jr., Philadelphia, serving as moderator. Collaborators will include William Thomas Fitts, Jr., Richard A. Kern, George P. Rosemond, Francis G. Wood, all of Philadelphia.

A panel discussion on diverticulitis will follow, from 3:30 to 5 p.m., with collaborators Allen M. Boyden, Portland, Oregon, Paul H. T. Thorlak-

son, Winnipeg, Rupert B. Turnbull, Jr., Cleveland. Moderator is John M. Waugh of Rochester, Minnesota. Other general sessions follow:

Tuesday, November 16

1:30–3:00 p.m.—Panel Discussion on Hypothermia.
Moderator: WILFRED G. BIGELOW, Toronto.
Collaborators: F. JOHN LEWIS, Minneapolis; WILLIAM H. MULLER, JR., Los Angeles; HENRY SWAN, Denver.
2:00–5:00 p.m.—Symposium on Trauma.
3:30–5:00 p.m.—Panel Discussion on Hormonal Balance in Surgery.
Moderator: HAROLD A. ZINTEL, Philadelphia.
Collaborators: CHARLES ECKERT, St. Louis, JAMES D. HARDY, Memphis, J. HARTWELL HARRISON, Boston.

Wednesday, November 17

1:30–3:00 p.m.—Clinicopathology Conference. JOHN M. PEARCE, New York, Moderator.
2:00–5:00 p.m.—Symposium on Cancer.
3:30–5:00 p.m.—Panel Discussion on Peripheral Arterial Disease.
Moderator: MICHAEL E. DEBAKEY, Houston.
Collaborators: FREDERICK W. COOPER, JR., Emory University; GEZA DETAKATS, Chicago; FIORINDO A. SIMEONE, Cleveland.

Thursday, November 18

1:30–3:00 p.m.—Panel Discussion on The Use and Abuse of Antibiotics in Therapy.
Moderator: WILLIAM A. ALTEMEIER, Cincinnati.
Collaborators: HARRY S. MORTON, Montreal; EDWIN J. PULASKI, Lt. Col., Washington, D.C.; WILLIAM R. SANDUSKY, Charlottesville, Va.

POSTGRADUATE COURSES

Because seating space for the postgraduate courses will be limited, it is important to make reservations in advance. An outline in brief is presented here. The September issue will carry more details of these courses:

Cardiovascular Surgery. JOHN H. GIBBON, JR., Philadelphia, Chairman.
Preoperative and Postoperative Care. JONATHAN E. RHOADS, Philadelphia, Chairman.
Surgery of the Lower Esophagus, Stomach, and Duodenum. REGINALD H. SMITHWICK, Boston, Chairman.
Diseases of the Liver, Biliary Tract and Pancreas. NATHAN A. WOMACK, Chapel Hill, Chairman.

For Surgical Specialties:
Orthopedic Surgery—Lower Extremity Amputations and Prostheses. HARRY D. MORRIS, New Orleans, Chairman
Thoracic Surgery—Surgical Aspects of Pulmonary Disease RICHARD H. OVERHOLT, Brookline, Mass., Chairman.
Trauma Committee—Combined Injuries to the Extremities. HARRISON L. MCLAUGHLIN, New York and HAROLD A. ZINTEL, Philadelphia, Co-Chairmen.
Gynecology and Obstetrics. THADDEUS L. MONTGOMERY, Philadelphia, Chairman.

The official registration form for postgraduate courses may be obtained from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

ADVANCE REGISTRATION

Because earlier registration insures more desirable hotel and transportation accommodations, and better assurance of acceptance in the postgraduate course of your choice, it is advisable to register as soon as possible. Official registration forms are now available from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

No registration fee is charged Fellows whose dues are paid as of December 31, 1953; no registration fee is required of Initiates, Junior Candidates or Surgical Residents whose applications are accompanied by letter of identification from the chief surgeon or hospital administrator. Non-Fellows will be charged $20.00 and members of the Federal Services, $10.00.

HOTEL RESERVATIONS

Official forms for hotel reservations must be obtained from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.